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Jon W Dudas

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Andrew James		Woodhead		Cambridge, United Kingdom	
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
PHARMACEUTICAL COMPOUNDS					
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ENCLOSED APPLICATION PARTS (check all that apply)					
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<input checked="" type="checkbox"/> Application Data Sheet. See 37 CFR 1.76		<input type="checkbox"/> CD(s), Number		<div style="border: 1px solid black; padding: 2px; display: inline-block;"></div>	
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Respectfully submitted,

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Date

07/03/03

TYPED or PRINTED NAME

Philip E. Hansen

REGISTRATION NO.

32,700

(if appropriate)

Docket Number:

2245.002

TELEPHONE

(518) 452-5600

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Applicant: Andrew James Woodhead

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PHARMACEUTICAL COMPOUNDS

This invention relates to pyrazole compounds that inhibit or modulate the activity of cyclin dependent kinases (CDK), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by cyclin dependent kinases, and to novel compounds having cyclin dependent kinase inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II*, Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.*, 9:576-596 (1995); Knighton, *et al.*, *Science*, 253:407-414 (1991); Hiles, *et al.*, *Cell*, 70:419-429 (1992); Kunz, *et al.*, *Cell*, 73:585-596 (1993); Garcia-Bustos, *et al.*, *EMBO J.*, 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins

occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

The process of eukaryotic cell division may be broadly divided into a series of sequential phases termed G1, S, G2 and M. Correct progression through the various phases of the cell cycle has been shown to be critically dependent upon the spatial and temporal regulation of a family of proteins known as cyclin dependent kinases (cdks) and a diverse set of their cognate protein partners termed cyclins. Cdk1 is cdc2 (also known as cdk1) homologous serine-threonine kinase proteins that are able to utilise ATP as a substrate in the phosphorylation of diverse polypeptides in a sequence dependent context. Cyclins are a family of proteins characterised by a homology region, containing approximately 100 amino acids, termed the "cyclin box" which is used in binding to, and defining selectivity for, specific cdk partner proteins.

Modulation of the expression levels, degradation rates, and activation levels of various cdks and cyclins throughout the cell cycle leads to the cyclical formation of a series of cdk/cyclin complexes, in which the cdks are enzymatically active. The formation of these complexes controls passage through discrete cell cycle checkpoints and thereby enables the process of cell division to continue. Failure to satisfy the pre-requisite biochemical criteria at a given cell cycle checkpoint, *i.e.* failure to form a required cdk/cyclin complex, can lead to cell cycle arrest and/or cellular apoptosis. Aberrant cellular proliferation, as manifested in cancer, can often be attributed to loss of correct cell cycle control. Inhibition of cdk enzymatic

activity therefore provides a means by which abnormally dividing cells can have their division arrested and/or be killed. The diversity of cdks, and cdk complexes, and their critical roles in mediating the cell cycle, provides a broad spectrum of potential therapeutic targets selected on the basis of a defined biochemical rationale.

- 5 Progression from the G1 phase to the S phase of the cell cycle is primarily regulated by cdk2, cdk3, cdk4 and cdk6 via association with members of the D and E type cyclins. The D-type cyclins appear instrumental in enabling passage beyond the G1 restriction point, where as the cdk2/cyclin E complex is key to the transition from the G1 to S phase. Subsequent progression through S phase and entry into G2 is thought to require the cdk2/cyclin A complex. Both mitosis, and the G2 to M phase transition which triggers it, are regulated by complexes of cdk1 and the A and B type cyclins.

- 15 During G1 phase Retinoblastoma protein (Rb), and related pocket proteins such as p130, are substrates for cdk(2, 4, & 6)/cyclin complexes. Progression through G1 is in part facilitated by hyperphosphorylation, and thus inactivation, of Rb and p130 by the cdk(4/6)/cyclin-D complexes. Hyperphosphorylation of Rb and p130 causes the release of transcription factors, such as E2F, and thus the expression of genes necessary for progression through G1 and for entry into S-phase, such as the gene for cyclin E. Expression of cyclin E facilitates formation of the cdk2/cyclin E complex which amplifies, or maintains, E2F levels via further phosphorylation of Rb. The cdk2/cyclin E complex also phosphorylates other proteins necessary for DNA replication, such as NPAT, which has been implicated in histone biosynthesis. G1 progression and the G1/S transition are also regulated via the mitogen stimulated Myc pathway, which feeds into the cdk2/cyclin E pathway. Cdk2 is also connected to the p53 mediated DNA damage response pathway via p53 regulation of p21 levels. p21 is a protein inhibitor of cdk2/cyclin E and is thus capable of blocking, or delaying, the G1/S transition. The cdk2/cyclin E complex may thus represent a point at which biochemical stimuli from the Rb, Myc and p53 pathways are to some degree integrated. Cdk2 and/or the cdk2/cyclin E complex therefore

represent good targets for therapeutics designed at arresting, or recovering control of, the cell cycle in aberrantly dividing cells.

The exact role of cdk3 in the cell cycle is not clear. As yet no cognate cyclin partner has been identified, but a dominant negative form of cdk3 delayed cells in G1, thereby suggesting that cdk3 has a role in regulating the G1/S transition.

Although most cdks have been implicated in regulation of the cell cycle there is evidence that certain members of the cdk family are involved in other biochemical processes. This is exemplified by cdk5 which is necessary for correct neuronal development and which has also been implicated in the phosphorylation of several neuronal proteins such as Tau, NUDE-1, synapsin1, DARPP32 and the Munc18/Syntaxin1A complex. Neuronal cdk5 is conventionally activated by binding to the p35/p39 proteins. Cdk5 activity can, however, be deregulated by the binding of p25, a truncated version of p35. Conversion of p35 to p25, and subsequent deregulation of cdk5 activity, can be induced by ischemia, excitotoxicity, and β -amyloid peptide. Consequently p25 has been implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, and is therefore of interest as a target for therapeutics directed against these diseases.

Cdk7 is a nuclear protein that has cdc2 CAK activity and binds to cyclin H. Cdk7 has been identified as component of the TFIIF transcriptional complex which has RNA polymerase II C-terminal domain (CTD) activity. This has been associated with the regulation of HIV-1 transcription via a Tat-mediated biochemical pathway. Cdk8 binds cyclin C and has been implicated in the phosphorylation of the CTD of RNA polymerase II. Similarly the cdk9/cyclin-T1 complex (P-TEFb complex) has been implicated in elongation control of RNA polymerase II. PTEF-b is also required for activation of transcription of the HIV-1 genome by the viral transactivator Tat through its interaction with cyclin T1. Cdk7, cdk8, cdk9 and the P-TEFb complex are therefore potential targets for anti-viral therapeutics.

At a molecular level mediation of cdk/cyclin complex activity requires a series of stimulatory and inhibitory phosphorylation, or dephosphorylation, events. Cdk

phosphorylation is performed by a group of cdk activating kinases (CAKs) and/or kinases such as wee1, Myt1 and Mik1. Dephosphorylation is performed by phosphatases such as cdc25(a & c), pp2a, or KAP.

Cdk/cyclin complex activity may be further regulated by two families of endogenous cellular proteinaceous inhibitors: the Kip/Cip family, or the INK family. The INK proteins specifically bind cdk4 and cdk6. p16^{ink4} (also known as MTS1) is a potential tumour suppressor gene that is mutated, or deleted, in a large number of primary cancers. The Kip/Cip family contains proteins such as p21^{Cip1, Waf1}, p27^{Kip1} and p57^{Kip2}. As discussed previously p21 is induced by p53 and is able to inactivate the cdk2/cyclin(E/A) and cdk4/cyclin(D1/D2/D3) complexes. Atypically low levels of p27 expression have been observed in breast, colon and prostate cancers. Conversely over expression of cyclin E in solid tumours has been shown to correlate with poor patient prognosis. Over expression of cyclin D1 has been associated with oesophageal, breast, squamous, and non-small cell lung carcinomas.

The pivotal roles of cdks, and their associated proteins, in co-ordinating and driving the cell cycle in proliferating cells have been outlined above. Some of the biochemical pathways in which cdks play a key role have also been described. The development of monotherapies for the treatment of proliferative disorders, such as cancers, using therapeutics targeted generically at cdks, or at specific cdks, is therefore potentially highly desirable. Cdk inhibitors could conceivably also be used to treat other conditions such as viral infections, autoimmune diseases and neuro-degenerative diseases, amongst others. Cdk targeted therapeutics may also provide clinical benefits in the treatment of the previously described diseases when used in combination therapy with either existing, or new, therapeutic agents. Cdk targeted anticancer therapies could potentially have advantages over many current antitumour agents as they would not directly interact with DNA and should therefore reduce the risk of secondary tumour development.

Glycogen Synthase Kinase-3 (GSK3) is a serine-threonine kinase that occurs as two ubiquitously expressed isoforms in humans (GSK3 α & beta GSK3 β). GSK3 has

been implicated as having roles in embryonic development, protein synthesis, cell proliferation, cell differentiation, microtubule dynamics, cell motility and cellular apoptosis. As such GSK3 has been implicated in the progression of disease states such as diabetes, cancer, Alzheimer's disease, stroke, epilepsy, motor neuron disease and/or head trauma. Phylogenetically GSK3 is most closely related to the cyclin dependent kinases (CDKs).

The consensus peptide substrate sequence recognised by GSK3 is (Ser/Thr)-X-X-X-(pSer/pThr), where X is any amino acid (at positions (n+1), (n+2), (n+3)) and pSer and pThr are phospho-serine and phospho-threonine respectively (n+4).

- 10 GSK3 phosphorylates the first serine, or threonine, at position (n). Phospho-serine, or phospho-threonine, at the (n+4) position appear necessary for priming GSK3 to give maximal substrate turnover. Phosphorylation of GSK3 α at Ser21, or GSK3 β at Ser9, leads to inhibition of GSK3. Mutagenesis and peptide competition studies have led to the model that the phosphorylated N-terminus of GSK3 is able to
15 compete with phospho-peptide substrate (S/TXXXpS/pT) via an autoinhibitory mechanism. There are also data suggesting that GSK3 α and GSK3 β may be subtly regulated by phosphorylation of tyrosines 279 and 216 respectively. Mutation of these residues to a Phe caused a reduction in *in vivo* kinase activity. The X-ray crystallographic structure of GSK3 β has helped to shed light on all aspects of
20 GSK3 activation and regulation.

- GSK3 forms part of the mammalian insulin response pathway and is able to phosphorylate, and thereby inactivate, glycogen synthase. Upregulation of glycogen synthase activity, and thereby glycogen synthesis, through inhibition of GSK3, has thus been considered a potential means of combating type II, or non-
25 insulin-dependent diabetes mellitus (NIDDM): a condition in which body tissues become resistant to insulin stimulation. The cellular insulin response in liver, adipose, or muscle tissues, is triggered by insulin binding to an extracellular insulin receptor. This causes the phosphorylation, and subsequent recruitment to the plasma membrane, of the insulin receptor substrate (IRS) proteins. Further
30 phosphorylation of the IRS proteins initiates recruitment of phosphoinositide-3

kinase (PI3K) to the plasma membrane where it is able to liberate the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3). This facilitates co-localisation of 3-phosphoinositide-dependent protein kinase 1 (PDK1) and protein kinase B (PKB or Akt) to the membrane, where PDK1 activates PKB. PKB is able to phosphorylate, and thereby inhibit, GSK3 α and/or GSK3 β through phosphorylation of Ser9, or Ser21, respectively. The inhibition of GSK3 then triggers upregulation of glycogen synthase activity. Therapeutic agents able to inhibit GSK3 may thus be able to induce cellular responses akin to those seen on insulin stimulation. A further *in vivo* substrate of GSK3 is the eukaryotic protein synthesis initiation factor 2B (eIF2B). eIF2B is inactivated via phosphorylation and is thus able to suppress protein biosynthesis. Inhibition of GSK3, e.g. by inactivation of the "mammalian target of rapamycin" protein (mTOR), can thus upregulate protein biosynthesis. Finally there is some evidence for regulation of GSK3 activity via the mitogen activated protein kinase (MAPK) pathway through phosphorylation of GSK3 by kinases such as mitogen activated protein kinase activated protein kinase 1 (MAPKAP-K1 or RSK). These data suggest that GSK3 activity may be modulated by mitogenic, insulin and/or amino acid stimuli.

It has also been shown that GSK3 β is a key component in the vertebrate Wnt signalling pathway. This biochemical pathway has been shown to be critical for normal embryonic development and regulates cell proliferation in normal tissues. GSK3 becomes inhibited in response to Wnt stimuli. This can lead to the de-phosphorylation of GSK3 substrates such as Axin, the adenomatous polyposis coli (APC) gene product and β -catenin. Aberrant regulation of the Wnt pathway has been associated with many cancers. Mutations in APC, and/or β -catenin, are common in colorectal cancer and other tumours. β -catenin has also been shown to be of importance in cell adhesion. Thus GSK3 may also modulate cellular adhesion processes to some degree. Apart from the biochemical pathways already described there are also data implicating GSK3 in the regulation of cell division via phosphorylation of cyclin-D1, in the phosphorylation of transcription factors such as c-Jun, CCAAT/enhancer binding protein α (C/EBP α), c-Myc and/or other

substrates such as Nuclear Factor of Activated T-cells (NFATc), Heat Shock Factor-1 (HSF-1) and the c-AMP response element binding protein (CREB). GSK3 also appears to play a role, albeit tissue specific, in regulating cellular apoptosis.

The role of GSK3 in modulating cellular apoptosis, via a pro-apoptotic mechanism, may be of particular relevance to medical conditions in which neuronal apoptosis can occur. Examples of these are head trauma, stroke, epilepsy, Alzheimer's and motor neuron diseases, progressive supranuclear palsy, corticobasal degeneration, and Pick's disease. *In vitro* it has been shown that GSK3 is able to hyperphosphorylate the microtubule associated protein Tau. Hyperphosphorylation of Tau disrupts its normal binding to microtubules and may also lead to the formation of intra-cellular Tau filaments. It is believed that the progressive accumulation of these filaments leads to eventual neuronal dysfunction and degeneration. Inhibition of Tau phosphorylation, through inhibition of GSK3, may thus provide a means of limiting and/or preventing neurodegenerative effects.

WO 02/34721 from Du Pont discloses a class of indeno [1,2-c]pyrazol-4-ones as inhibitors of cyclin dependent kinases.

WO 01/81348 from Bristol Myers Squibb describes the use of 5-thio-, sulfinyl- and sulfonylpyrazolo[3,4-b]-pyridines as cyclin dependent kinase inhibitors.

WO 00/62778 also from Bristol Myers Squibb discloses a class of protein tyrosine kinase inhibitors.

WO 01/72745A1 from Cyclacel describes 2-substituted 4-heteroaryl-pyrimidines and their preparation, pharmaceutical compositions containing them and their use as inhibitors of cyclin-dependant kinases (cdks) and hence their use in the treatment of proliferative disorders such as cancer, leukaemia, psoriasis and the like.

WO 99/21845 from Agouron describes 4-aminothiazole derivatives for inhibiting cyclin-dependent kinases (cdks), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical

compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.

WO 01/53274 from Agouron discloses as CDK kinase inhibitors a class of compounds which can comprise an amide-substituted benzene ring linked to an N-
5 containing heterocyclic group. Although indazole compounds are not mentioned generically, one of the exemplified compounds comprises an indazole 3-carboxylic acid anilide moiety linked via a methylsulfanyl group to a pyrazolopyrimidine.

WO 01/98290 (Pharmacia & Upjohn) discloses a class of 3-aminocarbonyl-2-carboxamido thiophene derivatives as protein kinase inhibitors. The compounds
10 are stated to have multiple protein kinase activity.

WO 01/53268 and WO 01/02369 from Agouron disclose compounds that mediate or inhibit cell proliferation through the inhibition of protein kinases such as cyclin dependent kinase or tyrosine kinase. The Agouron compounds have an aryl or heteroaryl ring attached directly or through a CH=CH or CH=N group to the 3-
15 position of an indazole ring.

WO 00/39108 (Du Pont Pharmaceuticals) describes a broad class of heterocyclic compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa and thrombin. The compounds are stated to be useful as anticoagulants or for the prevention of thromboembolic disorders.

20 Summary of the Invention

The invention provides compounds that have cyclin dependent kinase inhibiting or modulating activity and glycogen synthase kinase-3 (GSK3) inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the kinases.

25 Accordingly, in one aspect, the invention provides a compound of the formula (I) as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase or glycogen synthase kinase-3.

The invention also provides novel compounds of the formula (I) as defined herein.

The invention also provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase or glycogen synthase kinase-3.

In a further aspect, the invention provides a method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase or glycogen synthase kinase-3, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

10 This invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I) as defined herein in an amount effective in inhibiting abnormal cell growth.

This invention further provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of the formula (I) as defined herein in an amount effective to inhibit cdk2 or glycogen synthase kinase-3 activity.

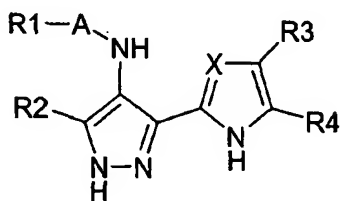
In another aspect, the invention provides a method of inhibiting a cyclin dependent kinase or glycogen synthase kinase-3, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

The invention further provides a method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase or glycogen synthase kinase-3 using a compound of the formula (I) as defined herein.

In a further aspect, the invention provides a pharmaceutical composition comprising a novel compound of the formula (I) as hereinbefore defined and a pharmaceutically acceptable carrier.

The invention also provides compounds of the formula (I) for use in medicine.

The compounds of the invention are represented by the general formula (I):



wherein

- 5 X is CR⁵ or N;
- A is a bond or $-(CH_2)_m-(B)_n$;
- B is C=O, NR⁸(C=O) or O(C=O) wherein R⁸ is hydrogen or C₁₋₄ hydrocarbyl optionally substituted by hydroxy or C₁₋₄ alkoxy;
- m is 0, 1 or 2;
- 10 n is 0 or 1;
- R¹ is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C₁₋₈ hydrocarbyl group;
- R² is hydrogen, halogen, methoxy, or a C₁₋₄ hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy;
- 15 R³ and R⁴ are the same or different and each is selected from hydrogen, optionally substituted C₁₋₈ hydrocarbyl and carbocyclic or heterocyclic groups having from 3 to 12 ring members;
- or R³ and R⁴ together with the carbon atoms to which they are attached form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7
- 20 ring members of which up to 3 can be heteroatoms selected from N, O and S; and
- R⁵ is hydrogen, a group R² or a group R¹⁰ wherein R¹⁰ is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹,
- 25 X¹C(X²)X¹, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C₁₋

4 hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

5 X^1 is O, S or NR^c and X^2 is =O, =S or = NR^c .

In formula (I), X can be CR^5 or N. In one particular embodiment, X is N. In another particular embodiment, X is CH.

When A is a bond or a group $-(CH_2)_m-(B)_n-$ wherein n is 0, X can be N or CR^5 wherein R^5 is hydrogen or a group R^{10} .

10 When A is a bond or a group $-(CH_2)_m-(B)_n-$ wherein n is 1, it is preferred that X is N or CR^5 wherein R^5 is hydrogen or a group R^2 .

Where R^5 is other than hydrogen, more particularly when n is 1, it is preferably a small substituent containing no more than 14 atoms, for example a C_{1-4} alkyl or cycloalkyl group such as methyl, ethyl, propyl and butyl, or cyclopropyl and

15 cyclobutyl.

A is a bond or $-(CH_2)_m-(B)_n-$ wherein B is $C=O$, $NR^g(C=O)$, m is 0, 1 or 2; and n is 0 or 1. In one preferred group of compounds of the invention, m is 0 or 1, n is 1 and B is $C=O$. More preferably, m is 0, n is 1 and B is $C=O$. It is presently preferred that when B is $NR^g(C=O)$, R^g is hydrogen.

20 It will be appreciated that the moiety R^1-A-NH linked to the 4-position of the pyrazole ring can take the form of an amine $R^1-(CH_2)_m-NH$, an amide $R^1-(CH_2)_m-C(=O)NH$, a urea $R^1-(CH_2)_m-NHC(=O)NH$ or a carbamate $R^1-(CH_2)_m-OC(=O)NH$ wherein in each case m is 0, 1 or 2, preferably 0 or 1 and most preferably 0.

R^1 is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C_{1-8} hydrocarbyl group. Examples of carbocyclic or heterocyclic groups, and optionally substituted hydrocarbyl groups are set out below.

25

R^2 is hydrogen, halogen, methoxy, or a C_{1-4} hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy. Preferably R^2 is hydrogen, chlorine or methyl, and most preferably R^2 is hydrogen.

In formula (I), according to one embodiment, R^3 and R^4 can be the same or
 5 different and each can be selected from hydrogen, optionally substituted C_{1-8} hydrocarbyl and carbocyclic or heterocyclic groups having from 3 to 12 ring members.

In another embodiment, R^3 and R^4 together with the carbon atoms to which they are attached form a fused carbocyclic or heterocyclic ring having from 5 to 7 ring
 10 members of which up to 3 can be heteroatoms selected from N, O and S.

The fused carbocyclic or heterocyclic ring can be optionally substituted by 0-4 groups R^{10} as defined herein.

Where reference is made herein to carbocyclic and heterocyclic groups, whether in
 15 relation to R^1 , R^3 and R^4 or a fused ring defined by R^3 and R^4 , or in relation to any other moiety, the carbocyclic or heterocyclic ring can, unless the context indicates otherwise, be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having
 20 from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino,
 25 mono- or di- C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

30 X^1 is O, S or NR^c and X^2 is =O, =S or = NR^c .

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10} . In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include

5 carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10} .

References to "carbocyclic" and "heterocyclic" groups as used herein, either with

10 regard to the group R^1 , R^3 , R^4 or any other substituent group, unless the context indicates otherwise include both aromatic and non-aromatic ring systems. Thus, for example, the term "carbocyclic and heterocyclic groups having from 3 to 12 ring members" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated carbocyclic and heterocyclic ring systems.

15 The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring

20 systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may be attached by the aromatic ring, or to a non-aromatic ring. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{10} as defined herein.

25 The term non-aromatic group embraces unsaturated ring systems without aromatic character, partially saturated and fully saturated carbocyclic and heterocyclic ring systems. The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a $C=C$, $C\equiv C$ or $N=C$ bond. The term "fully

saturated" refers to rings where there are no multiple bonds between ring atoms.

Saturated carbocyclic groups include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cycloheptenyl and cyclooctenyl.

- 5 Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four
10 heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in
15 the heteroaryl group, including any amino group substituents of the ring, will be less than five.

- Examples of heteroaryl groups include but are not limited to pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl,
20 thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, indolyl, isoindolyl, indoliziny, indoliny, isoindoliny, puriny (e.g., adenine, guanine), indazolyl, benzodioxolyl,
25 chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinoliziny, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

- Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthyl, tetrahydroisoquinolinyl,
30 tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-

benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indolinyl and indanyl.

In the context of the R^1 group, particular heteroaryl groups include furanyl, indolyl, oxazolyl, isoxazolyl, pyridyl, quinolinyl, 2,3-dihydro-benzo[1,4]dioxine,
 5 benzo[1,3]dioxole, imidazolyl and thiophenyl. More particular R^1 heteroaryl groups include furanyl, indolyl, oxazolyl, isoxazolyl, pyridyl, quinolinyl, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole. Presently preferred groups are furanyl and 2,3-dihydro-benzo[1,4]dioxine groups.

10 Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

In the context of the R^1 group, preferred aryl groups are those based on a phenyl ring.

In the context of the R^3 and R^4 groups, preferred aryl groups are based on a phenyl ring.

15 Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocyclic groups can contain, for example,
 20 cyclic ether moieties (e.g. as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene)), cyclic sulphoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine).

Particular examples include morpholine, piperidine (e.g. 1-piperidinyl, 2-
 25 piperidinyl 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl),

imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include morpholine, and N-alkyl piperazines.

5

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, as well as cyclohexadienyl, cyclooctatetraene, tetrahydronaphthenyl and decalanyl.

- 10 In the context of R^1 groups, preferred non-aromatic carbocyclic groups include monocyclic cycloalkyl groups such as cyclohexyl and cyclopentyl, particularly cyclohexyl.

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

- 15 In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms.
- 20 Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or
- 25 hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl

groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2} hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 and C_8 hydrocarbyl groups.

- 5 The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} alkyl groups, such as C_{1-4} alkyl groups (e.g. C_{1-3} alkyl groups or C_{1-2} alkyl groups).
- 10

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C_{3-6} cycloalkyl groups.

- 15 Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C_{2-6} alkenyl groups, such as C_{2-4} alkenyl groups.

- 20 Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C_{3-6} cycloalkenyl groups.

- Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C_{2-6} alkynyl groups, such as C_{2-4} alkynyl groups.
- 25

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl groups.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

- 5 When present, a hydrocarbyl group can be optionally substituted by one or more substituents selected from hydroxy, oxo, alkoxy, carboxy, halogen, cyano, nitro, amino, mono- or di-C₁₋₄ hydrocarbylamino, and monocyclic or bicyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine.
- 10 Thus, for example, the substituent can be a partially fluorinated or perfluorinated group such as trifluoromethyl. In one embodiment preferred substituents include monocyclic carbocyclic and heterocyclic groups having 3-7 ring members.

- One or more carbon atoms of a hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹ wherein X¹ and X² are as
- 15 hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S),
 - 20 amides, esters, thioamides and thioesters (C replaced by X¹C(X²) or C(X²)X¹), sulphones and sulfoxides (C replaced by SO or SO₂) and amines (C replaced by NR^c).

- Where an amino group has two hydrocarbyl substituents, they may, together with the nitrogen atom to which they are attached, and optionally with another
- 25 heteroatom such as nitrogen, sulphur, or oxygen, link to form a ring structure of 4 to 7 ring members.

The definition "R^a-R^b" as used herein, either with regard to substituents present on a carbocyclic or heterocyclic moiety, or with regard to other substituents present at other locations on the compounds of the formula (I), includes *inter alia* compounds

wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, OC(NR^c), SC(NR^c), $NR^cC(NR^c)$, C(O)O, C(O)S, C(O) NR^c , C(S)O, C(S)S, C(S) NR^c , C(NR^c)O, C(NR^c)S, C(NR^c) NR^c , OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, OC(NR^c)O, SC(NR^c)O, $NR^cC(NR^c)O$,
 5 OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, OC(NR^c)S, SC(NR^c)S, $NR^cC(NR^c)S$, OC(O) NR^c , SC(O) NR^c , $NR^cC(O)NR^c$, OC(S) NR^c , SC(S) NR^c , $NR^cC(S)NR^c$, OC(NR^c) NR^c , SC(NR^c) NR^c , $NR^cC(NR^c)NR^c$, S, SO, SO₂, NR^c , SO₂ NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and
 10 heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C₁₋₈ hydrocarbyl group optionally substituted as hereinbefore defined. Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

In the compounds of the formula (I), R^3 and R^4 , together with the carbon atoms to
 15 which they are attached, can form a fused heterocyclic or carbocyclic group having from 5 to 7 ring members. The fused heterocyclic or carbocyclic group can be aromatic or non-aromatic but preferably is aromatic. In one preferred group of compounds, R^3 and R^4 together with the carbon atoms to which they are attached form a fused carbocyclic group having from 5 to 7 ring members.

Where R^3 and R^4 form a carbocyclic or heterocyclic ring as hereinbefore defined,
 20 fused five and six membered groups are particularly preferred. Examples of fused heterocyclic rings include five and six membered rings such as thiazolo, isothiazolo, oxazolo, isoxazolo, pyrrolo, pyrido, thieno, furano, pyrimido, pyrazolo, pyrazino, and imidazolo fused rings. It is preferred that the fused heterocyclic
 25 group is selected from six membered ring groups, one particularly preferred group being the pyrido group.

Examples of fused carbocyclic rings include five and six membered rings such as benzo, dihydro or tetrahydro-benzo and cyclopenta- fused rings. Six membered rings are preferred. One particularly preferred group is the benzo group.

The fused carbocyclic or heterocyclic group can be optionally substituted by one or more groups R^{10} as hereinbefore defined.

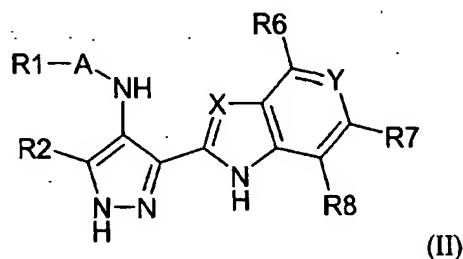
- In one embodiment, the substituents on the fused carbocyclic or heterocyclic group may be selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 7 (typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c , X^1 and X^2 are as hereinbefore defined.
- Preferred R^{10} groups on the fused carbocyclic or heterocyclic group formed by R^3 and R^4 include halogen, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic group having 3-7 ring members and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, heterocyclic group with 3-7 ring members.

- The group R^1 can be an unsubstituted or substituted carbocyclic or heterocyclic group in which one or more substituents can be selected from the group R^{10} as hereinbefore defined. In one embodiment, the substituents on R^1 may be selected from the group R^{10a} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $X^3C(X^4)$, $C(X^4)X^3$, $X^3C(X^4)X^3$, S, SO, or SO_2 , and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy; wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , $X^3C(X^4)$, $C(X^4)X^3$ or $X^3C(X^4)X^3$; X^3 is O or S; and X^4 is =O or =S.

More particularly, the substituents on R^1 may be selected from halogen, hydroxy, trifluoromethyl, a group R^a-R^b wherein R^a is a bond or O, and R^b is selected from hydrogen and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxyl and halogen.

- 5 The moiety R^1 may be substituted by more than one substituent. Thus, for example, there may be 1 or 2 or 3 or 4 substituents. In one embodiment, where R^1 is a six membered ring (e.g. a carbocyclic ring such as a phenyl ring), there may be two or three substituents and these may be located at the 2-, 3-, 4- or 6-positions around the ring. By way of example, a phenyl group R^1 may be 2,6-disubstituted, 2,3-
- 10 disubstituted, 2,4-disubstituted 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted. More particularly, a phenyl group R^1 may be disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and R^a-R^b , where R^a is O and R^b is C_{1-4} alkyl, with fluorine being a particular substituent.

- One preferred group of compounds of the invention is represented by the formula
- 15 (II):



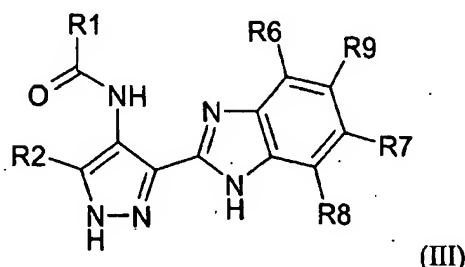
- wherein R^1 , R^2 and X are as hereinbefore defined;
- Y is N or CR^9 wherein R^9 is hydrogen or a group R^{10} ; and
- R^6 , R^7 and R^8 are the same or different and each is hydrogen or a group R^{10} as
- 20 hereinbefore defined.

In one sub-group of compounds of the formula (II), X is N.

In another sub-group of compounds of the formula (II), Y is CR^9 .

When Y is N, it is preferred that R^6 is other than amino.

In one embodiment, the compounds of the invention are represented by the formula (III):



- 5 wherein R¹, R² and R⁶ to R⁹ are as hereinbefore defined.

Within formula (III), it is preferred that R² is hydrogen or C₁₋₄ alkyl, and more typically R² is hydrogen.

- Within the group of compounds defined by the formula (III), R¹ is preferably 2,3 disubstituted, 2,6 disubstituted or 2,4,6, trisubstituted phenyl or 2, 3-dihydro-
10 benzo[1,4]dioxine, where the substituents are selected from halogen and C₁₋₄ alkoxy.

More preferably R¹ is selected from 2,6-difluorophenyl, 2-fluoro-6-methoxyphenyl, 2-chloro-6-fluorophenyl, 2,6-dichlorophenyl, 2,4,6-trifluorophenyl, 2,6-difluoro-4-methoxyphenyl, and 2,3-dihydro-benzo[1,4]dioxine.

- 15 One particularly preferred group R¹ is 2,6-difluorophenyl.

- In one preferred group of compounds of the formula (III), R⁶ to R⁹ are each hydrogen or are selected from halogen (e.g. fluorine or chlorine), cyano, hydroxy, trifluoromethyl, nitro, a group R^a-R^b wherein R^a is a bond, O, CO or C(X²)X¹ and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring
20 members, more preferably 4 to 7 ring members, and a C₁₋₈ hydrocarbyl group, more preferably a C₁₋₄ hydrocarbyl group, optionally substituted by one or more substituents selected from hydroxy, C₁₋₄ acyloxy, mono- or di-C₁₋₄ hydrocarbylamino, heterocyclic groups having from 3 to 12 ring members, more

preferably 4 to 7 ring members; where R^c is selected from hydrogen and C_{1-4} hydrocarbonyl, X^1 is O, NR^c and X^2 is $=O$.

More preferably, R^6 to R^9 are each hydrogen or a group R^a-R^b wherein R^a is a bond,
 5 CO , $C(X^2)X^1$ and R^b is selected from hydrogen, saturated heterocyclic groups having 5 or 6 ring members e.g. pyrrolidine, N-methyl piperazine or morpholine, and a C_{1-4} hydrocarbonyl group, optionally substituted by one or more substituents selected from mono- or di- C_{1-4} hydrocarbonylamino, saturated heterocyclic groups having 5 or 6 ring members e.g. N-methyl piperazine or morpholine; where X^1 is
 10 NR^c , X^2 is $=O$ and R^c is selected from hydrogen and C_{1-4} hydrocarbonyl.

Whereas each of R^6 to R^9 can be hydrogen or a substituent R^{10} , it is preferred that at least one, more preferably at least two, and more typically at least three of R^6 to R^9 are hydrogen. In one particular embodiment, one of R^6 to R^9 is a group R^{10} and the others are each hydrogen. For example, R^6 can be a substituent group R^{10} and R^7 to
 15 R^9 can each be hydrogen, or R^9 can be a substituent group R^{10} and R^6 to R^8 can each be hydrogen.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example of the groups R^1 may be combined with each general and specific preference, embodiment and example of the groups R^2 and/or
 20 R^3 and that all such combinations are embraced by this application.

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less
 25 than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

Particular compounds of the invention are as illustrated in the examples below.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

Compounds of the formula may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group $-C(=O)OR$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and $-C(=O)OPh$. Examples of acyloxy (reverse ester) groups are represented by $-OC(=O)R$, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, $-OC(=O)Ph$, and $-OC(=O)CH_2Ph$.

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group ($-C(=O)OR$) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups ($-C(=O)OH$) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula $-C(=O)OR$ wherein R is:

C_{1-7} alkyl

(e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);

C_{1-7} aminoalkyl

(e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and

- acyloxy-C₁₋₇alkyl
 (e.g., acyloxymethyl;
 acyloxyethyl;
 pivaloyloxymethyl;
 5 acetoxymethyl;
 1-acetoxyethyl;
 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl;
 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;
 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
 10 1-cyclohexyl-carbonyloxyethyl;
 cyclohexyloxy-carbonyloxymethyl;
 1-cyclohexyloxy-carbonyloxyethyl;
 (4-tetrahydropyranyloxy) carbonyloxymethyl;
 1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
 15 (4-tetrahydropyranyl)carbonyloxymethyl; and
 1-(4-tetrahydropyranyl)carbonyloxyethyl).

- Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be
 20 a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Where the compounds of the formula (I) contain chiral centres, all individual optical forms such as enantiomers, epimers and diastereoisomers, as well as racemic mixtures of the compounds are within the scope of formula (I).

- 25 The compounds of the formula (I) are inhibitors of cyclin dependent kinases. For example, compounds of the invention have activity against CDK1, CDK2, CDK3, CDK5, CDK6 and CDK7 kinases.

Compounds of the invention also have activity against glycogen synthase kinase-3 (GSK-3).

As a consequence of their activity in modulating or inhibiting CDK kinases and glycogen synthase kinase, they are expected to be useful in providing a means of arresting, or recovering control of, the cell cycle in abnormally dividing cells. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. It is also envisaged that the compounds of the invention will be useful in treating conditions such as viral infections, autoimmune diseases and neurodegenerative diseases for example.

CDKs play a role in the regulation of the cell cycle, apoptosis, transcription, differentiation and CNS function. Therefore, CDK inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation such as cancer. In particular RB+ve tumours may be particularly sensitive to CDK inhibitors.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma, ; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

CDKs are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore CDK inhibitors could also be useful in the treatment of

the following diseases other than cancer; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune
 5 mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and
 10 cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive
 15 rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

It has also been discovered that some cyclin-dependent kinase inhibitors can be used in combination with other anticancer agents. For example, the cytotoxic activity of cyclin-dependent kinase inhibitor flavopiridol, has been used with other anticancer agents in combination therapy.

20 Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung
 25 carcinomas.

The activity of the compounds of the invention as inhibitors of cyclin dependent kinases and glycogen synthase kinase-3 can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC_{50} value. Preferred compounds of the present invention

are compounds having an IC_{50} value of less than 1 micromole, more preferably less than 0.1 micromole.

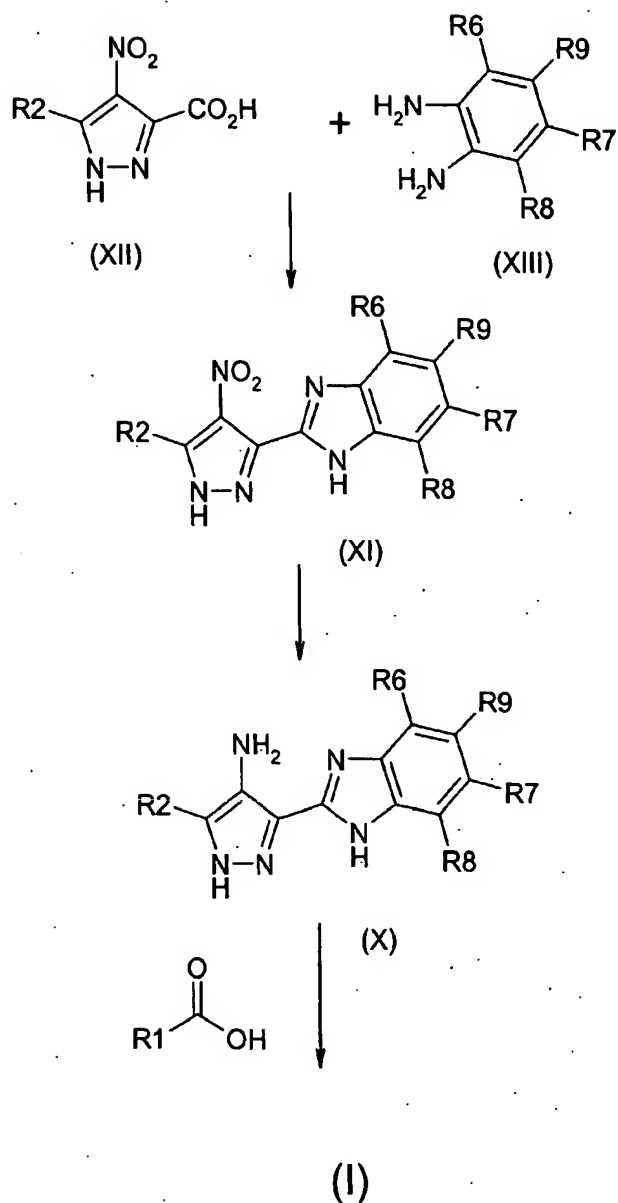
Methods for the Preparation of Compounds of the Formula (I)

5 Compounds of the formula (I) can be prepared in accordance with synthetic methods well known to the skilled person.

Compounds of the formula (I) wherein R^1 -A- forms an acyl group can be prepared as illustrated in Scheme 1 below.

As shown in Scheme 1, an amine of the formula (X) can be reacted with with a carboxylic acid, or reactive derivative thereof, of the formula R^1 -B- CO_2H under
10 standard amide formation conditions. Thus, for example, the coupling reaction between the carboxylic acid and the amine (X) can be carried out in the presence of a reagent of the type commonly used in the formation of peptide linkages.

Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan
et al, *J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)-
15 carbodiimide (EDC) (Sheehan *et al*, *J. Org. Chem.*, 1961, 26, 2525), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115,
4397) and phosphonium-based coupling agents such as 1-benzo-
triazolyloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et*
20 *al*, *Tetrahedron Letters*, 1990, 31, 205). Carbodiimide-based coupling agents are advantageously used in combination with 1-hydroxybenzotriazole (HOBt) (Konig *et al*, *Chem. Ber.*, 103, 708, 2024-2034). Preferred coupling reagents include EDC and DCC in combination with HOBt.



Scheme 1

(X)

The coupling reaction is typically carried out in a non-aqueous, non-protic solvent such as acetonitrile, dioxan, dimethylsulphoxide, dichloromethane, dimethylformamide or N-methylpyrrolidine, or in an aqueous solvent optionally

together with one or more miscible co-solvents. The reaction can be carried out at room temperature or, where the reactants are less reactive (for example in the case of electron-poor anilines bearing electron withdrawing groups such as sulphonamide groups) at an appropriately elevated temperature. The reaction may
5 be carried out in the presence of a non-interfering base, for example a tertiary amine such as triethylamine or *N,N*-diisopropylethylamine.

As an alternative, a reactive derivative of the carboxylic acid, e.g. an anhydride or acid chloride, may be used. Reaction with a reactive derivative such as an anhydride is typically accomplished by stirring the amine and anhydride at room temperature
10 in the presence of a base such as pyridine.

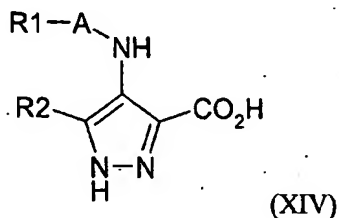
Amines of the formula (X) can be prepared by reduction of the corresponding nitro-compound of the formula (XI) under standard conditions. The reduction may be effected, for example by catalytic hydrogenation in the presence of a catalyst such as palladium on carbon in a polar solvent such as ethanol or dimethylformamide at
15 room temperature.

When X is nitrogen, the compounds of the formula (XI) can be prepared by reaction of a nitro-pyrazole carboxylic acid of the formula (XII) with a diamine of the formula (XIII). The reaction between the diamine (XIII) and carboxylic acid (XII) can be carried out in the presence of a reagent such as DCC or EDC in the presence
20 of HOBt as described above, under amide coupling conditions as described previously, to give an intermediate *ortho*-aminophenylamide (not shown) which is then cyclised to form the benzimidazole ring. The final cyclisation step is typically carried out by heating under reflux in the presence of acetic acid.

Diamines of the formula (XIII) can be obtained commercially or can be prepared
25 from appropriately substituted phenyl precursor compounds using standard chemistry and well known functional group interconversions, see for example, *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8),

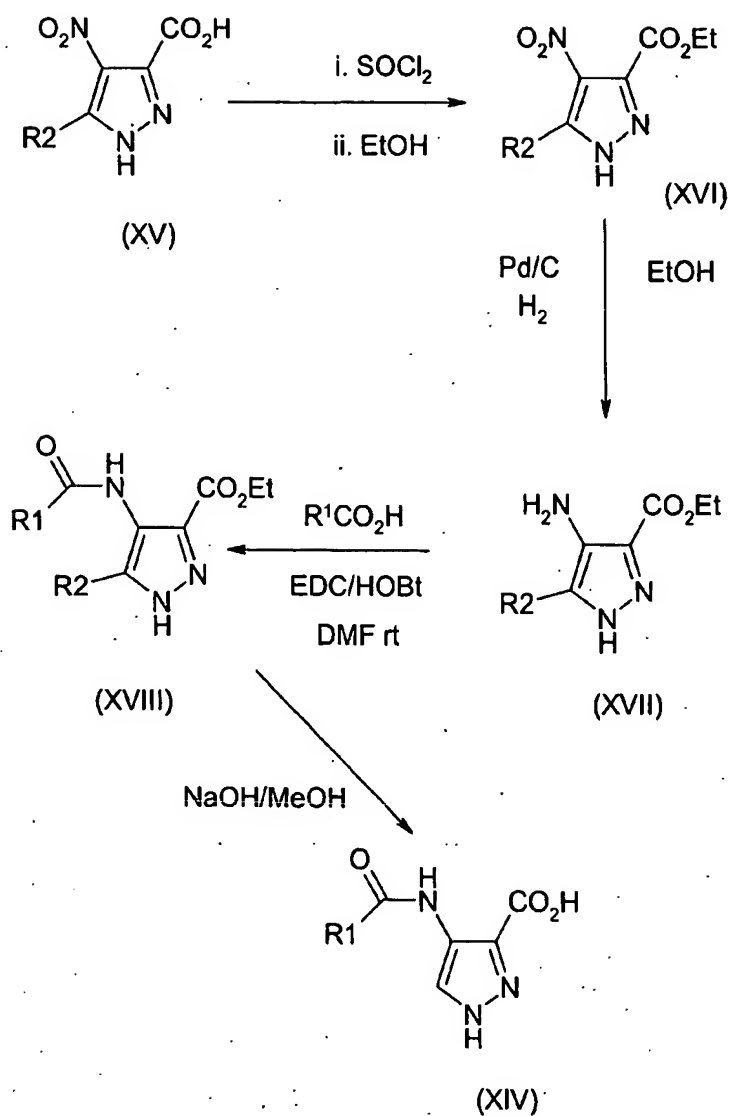
1995. Examples of methods of preparing diamines of the formula (XIII) are provided in the examples below.

The diamines of the formula (XIII) can also be reacted with carboxylic acids of the formula (XIV) to give compounds of the formula (I).



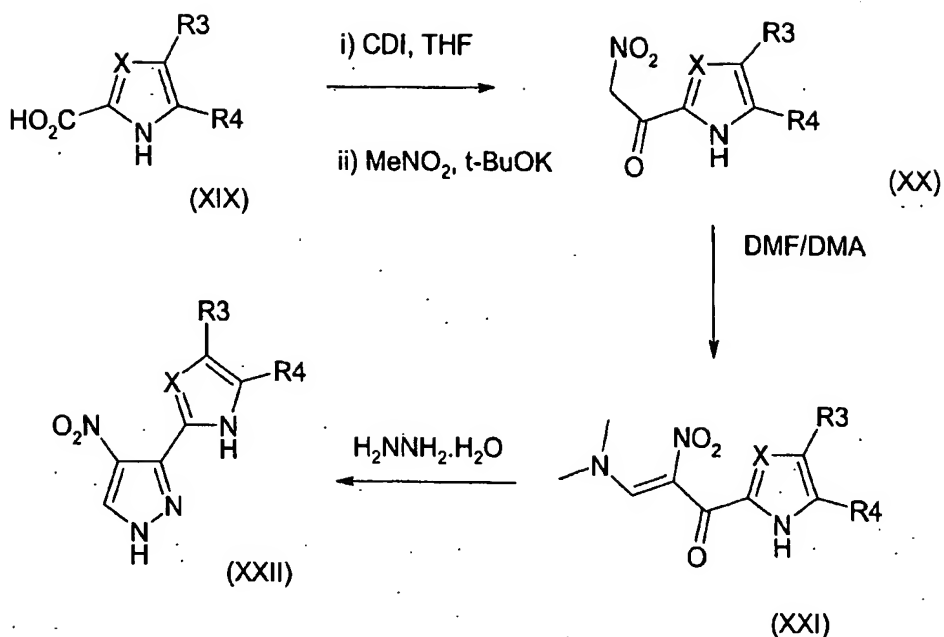
The reaction of the diamine (XIII) with the carboxylic acid (XIV) can be carried out under conditions analogous to those described above for preparing the nitro-compounds (XI). Carboxylic acids of the formula (XIV) can be prepared by the sequence of reactions shown in Scheme 2.

- 10 As shown in Scheme 2, a substituted or unsubstituted 4-nitro-3-pyrazole carboxylic acid (XV) can be esterified by reaction with thionyl chloride to give the acid chloride intermediate followed by reaction with ethanol to form the ethyl ester (XVI). Alternatively, the esterification can be carried out by reacting the alcohol and carboxylic acid in the presence of an acidic catalyst, one example of which is
- 15 thionyl chloride. The reaction is typically carried out at room temperature using the esterifying alcohol (e.g. ethanol) as the solvent. The nitro group can then be reduced using palladium on carbon according to standard methods to give the amine (XVII). The amine (XVII) is coupled with an appropriate carboxylic acid $R^1\text{-CO}_2\text{H}$ under amide forming conditions the same as or analogous to those described above
- 20 to give the amide (XVIII). The ester group of the amide (XVIII) can then be hydrolysed using an alkali metal hydroxide such as sodium hydroxide in a polar water miscible solvent such as methanol, typically at room temperature.



Scheme 2

A further synthetic route to compounds of the formula (I) is shown in Scheme 3 below.



Scheme 3

- As illustrated in scheme 3, a carboxylic acid of the formula (XIX) can be activated with 1,1'-carbonyl diimidazole in an appropriate aprotic solvent. Subsequent reaction with the anion of nitromethane gives a 2-nitroketone (XX) (Rudolph et al, *Org. Lett.*, 2001, 3(20), 3153-3155). Further reaction of a 2-nitroketone with dimethylformamide-dimethylacetal at elevated temperature gives an α,β -unsaturated ketone (XXI) (Jachak et al, *Montash. Chem.*, 1993, 124(2), 199-207), which upon heating with hydrazine hydrate gives a pyrazole of formula (XXII).
- 10 The procedure illustrated in Scheme 3 are of particular utility in the preparation of compounds when X is a group CR^5 .

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and

deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl),
 5 or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal (R-CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily
 10 regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyloxy amide (-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), or as a 2-(phenylsulphonyl)ethyloxy amide (-NH-Psec). Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulfonyl (tosyl)
 20 and methanesulfonyl (mesyl) groups and benzyl groups such as a *para*-methoxybenzyl (PMB) group. A carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇ haloalkyl ester (e.g., a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide. A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

Pharmaceutical Formulations

The invention also provides compounds of the formula (I) as hereinbefore defined
 30 in the form of pharmaceutical compositions.

- The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal,
- 5 subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

- 10 Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

- Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose,
- 15 sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable
- 20 crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

- 25 Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit TM type polymer) can be designed to release the active component at a desired location
5 within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which
10 may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active
15 compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

Compositions for topical use include ointments, creams, sprays, patches, gels,
20 liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for
25 injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administered in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

15 Methods of Treatment

It is envisaged that the compounds of the formula (I) will be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by cyclin dependent kinases. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include cytotoxic agents, agents that prevent cell proliferation or radiotherapy. Examples of such agents include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders and microtubule inhibitors, such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes and mitomycin C.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using the system and operating conditions set out below. Where chlorine is present, the mass quoted for the compound is for ³⁵Cl. The two systems were equipped with identical chromatography columns and were set up to run under the same operating conditions. The operating conditions used are also described below.

Platform system

System: Waters 2790/Platform LC

Mass Spec Detector: Micromass Platform LC

PDA Detector: Waters 996 PDA

Analytical conditions:

Eluent A: 5% CH₃CN in 95% H₂O (0.1% Formic Acid)

Eluent B: CH₃CN (0.1% Formic Acid)

5 Gradient: 10-95% eluent B

Flow: 1.2 ml/min

Column: Synergi 4µm Max-RP C₁₂, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage: 3.5 kV

10 Cone voltage: 30 V

Source Temperature: 120 °C

FractionLynx system

System: Waters FractionLynx (dual analytical/prep)

Mass Spec Detector: Waters-Micromass ZQ

15 PDA Detector: Waters 2996 PDA

Analytical conditions:

Eluent A: H₂O (0.1% Formic Acid)

Eluent B: CH₃CN (0.1% Formic Acid)

Gradient: 5-95% eluent B

20 Flow: 1.5 ml/min

Column: Synergi 4µm Max-RP C₁₂, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage: 3.5 kV

Cone voltage: 30 V

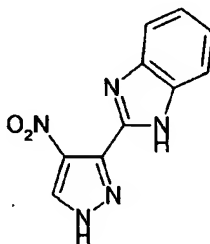
25 Source Temperature: 120 °C

Desolvation Temperature: 300 °C

The starting materials for each of the Examples are commercially available unless otherwise specified.

EXAMPLE 1

Synthesis of 2-(4-Nitro-1H-pyrazol-3-yl)-1H-benzimidazole



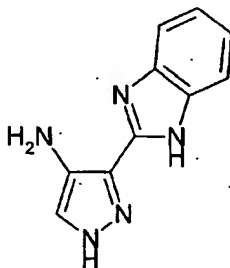
5

A mixture of *o*-phenylenediamine (1.51 g, 14.0 mmol), 4-amino-1H-pyrazole-3-carboxylic acid (2.00 g, 12.7 mmol), EDC (2.93 g, 15.3 mmol) and HOBt (2.08 g, 15.3 mmol) in DMF (70 mL) was stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo* and the residue dissolved in AcOH (150 mL) and heated at reflux for 3 h. The solvent was removed *in vacuo*, water (100 mL) added and the resultant solid collected by filtration washing with water. The solid was dried through azeotrope with toluene (3 x 150 mL) yielding 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole as a yellow solid (1.44 g, 50%). A 100 mg portion was purified by preparative LC/MS and following evaporation of product containing fractions gave 70 mg of the title compound. (LC/MS: R_f 1.72, $[M+H]^+$ 229.61).

15

EXAMPLE 2

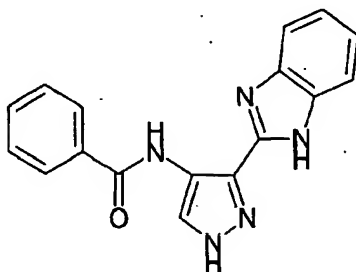
Synthesis of 3-(1H-Benzimidazol-2-yl)-1H-pyrazol-4-ylamine



A mixture of 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole (1.34 g, 5.85 mmol) and 10% Pd/C (0.13 g) in DMF (200 mL) was subjected to an atmosphere of hydrogen at room temperature for 36 h. The reaction mixture was filtered through a plug of Celite and reduced *in vacuo*. The residue was partitioned between EtOAc and water and the organic portion dried (MgSO₄), filtered and reduced *in vacuo*.
 5 The residue was azeotroped with toluene (3 x 150 mL) yielding 3-(1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine as a purple solid (0.32 g, 26%). (LC/MS: R_t 0.97, [M+H]⁺ 199.62).

EXAMPLE 3

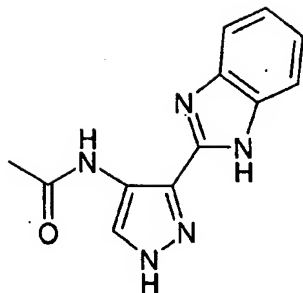
10 Synthesis of N-[3-(1H-Benzimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



A mixture of benzoic acid (34 mg, 0.28 mmol), 3-(1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (40.5 mg, 0.30 mmol) in DMF (5 mL) was stirred at room temperature for 24 h. The
 15 solvent was removed *in vacuo*, the crude product purified by preparative LC/MS and following reduction of the product-containing fractions N-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide was obtained as a brown solid (23 mg, 30%). (LC/MS: R_t 3.66, [M+H]⁺ 303.67).

EXAMPLE 4

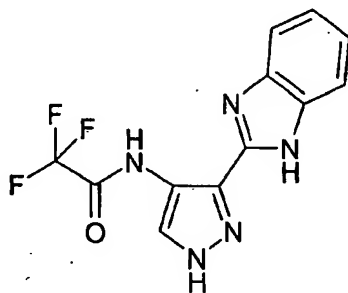
20 Synthesis of N-[3-(1H-Benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide



Acetic anhydride (27 μ l, 0.28 mmol) was added to a solution of 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol) in pyridine (5 mL) and the reaction mixture stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo* and the residue purified by flash column chromatography [SiO_2 , EtOAc-petrol (1:2.5, 2:1)] to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide as a brown crystalline solid (29 mg, 48%). (LC/MS: R_t 1.70, $[\text{M}+\text{H}]^+$ 241.64).

EXAMPLE 5

10 Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,2,2-trifluoroacetamide

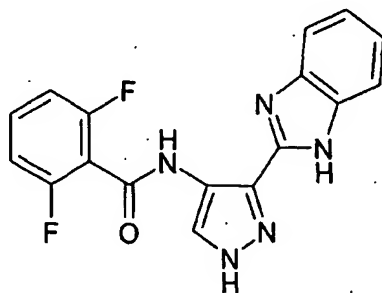


Trifluoroacetic anhydride (40 μ l, 0.28 mmol) was added to a solution of 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol) in pyridine (5 mL) and the reaction mixture stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo* and the residue purified by flash column chromatography [SiO_2 , EtOAc-petrol (1:2)] to afford N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-

2,2,2-trifluoro-acetamide as a cream solid (23 mg, 32%). (LC/MS: R_t 3.67, $[M+H]^+$ 295.63).

EXAMPLE 6

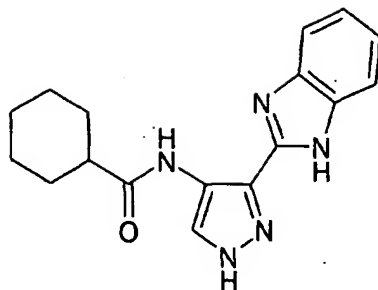
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-
5 benzamide



A mixture of 2,6-difluorobenzoic acid (43 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (40.5 mg, 0.30 mmol) in DMF (10 mL) was stirred at ambient temperature
10 for 24 h. The mixture was reduced *in vacuo*, water (30 mL) added and the resultant solid collected by filtration, dried in the vacuum oven and purified by flash column chromatography [SiO_2 , EtOAc-petrol (1:2, 1:1, 3:1)] affording N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (20 mg, 24%). (LC/MS: R_t 3.29, $[M+H]^+$ 339.64).

15 EXAMPLE 7

Synthesis of Cyclohexanecarboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-
4-yl]-amide

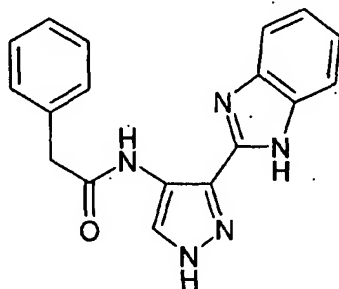


A mixture of cyclohexanecarboxylic acid (36 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMSO (2 mL) was stirred at ambient temperature for 24 h. The reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL) and the organic portion dried (MgSO₄), filtered and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO₂, EtOAc-petrol (1:4, 1:3, 1:2, 1:1)] affording cyclohexanecarboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide as an off-white solid (25 mg, 32%).

(LC/MS: R_t 3.59, [M+H]⁺ 310.16).

EXAMPLE 8

Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide

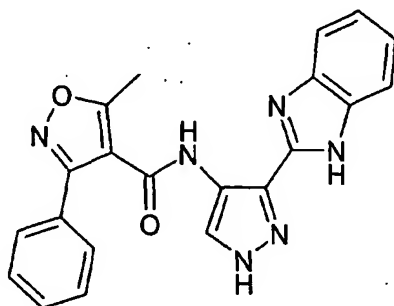


A mixture of phenylacetic acid (38 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMSO (2 mL) was stirred at ambient temperature for 24 h. The reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL) and the organic portion dried (MgSO₄), filtered and reduced *in vacuo*. The residue

was purified by flash column chromatography [SiO_2 , EtOAc-petrol (1:2, 1:1, 2:1)] to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide as a brown solid (15 mg, 19%). (LC/MS: R_t 3.26, $[\text{M}+\text{H}]^+$ 318.13).

EXAMPLE 9

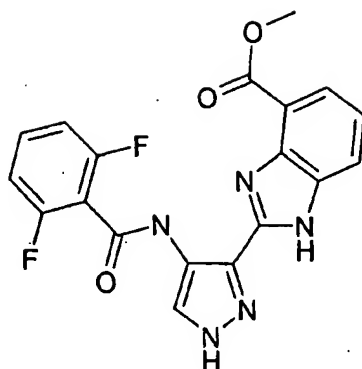
5 Synthesis of 5-Methyl-3-phenyl-isoxazole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



A mixture of 5-methyl-3-phenylisoxazole-4-carboxylic acid (57 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMSO (2 mL) was stirred at ambient temperature for 24 h. The reaction mixture was partitioned between EtOAc and water and the organic portion dried (MgSO_4), filtered and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2 , EtOAc-petrol (1:2, 1:1, 2:1)] affording 5-methyl-3-phenyl-isoxazole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a cream solid (15 mg, 16%). (LC/MS: R_t 3.73, $[\text{M}+\text{H}]^+$ 385.14).

EXAMPLE 10

Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester



Sodium methoxide (1.50 g, 27.7 mmol) was added to a solution of methyl-2-
 (acetylamino)-3-nitrobenzoate (1.0 g, 4.2 mmol) in MeOH (30 mL) and the mixture
 stirred at ambient temperature under nitrogen for 16 h. The reaction was cautiously
 5 acidified with concentrated hydrochloric acid then heated at reflux overnight,
 followed by evaporation and re-evaporation by toluene (2 x 30 mL). The residue
 was treated with CH₂Cl₂ (50 mL), the insoluble material removed through filtration
 and the filtrate reduced *in vacuo*. The residue was purified by flash column
 chromatography [SiO₂, EtOAc-hexane (1:4, 1:0)] affording methyl-2-amino-3-
 10 nitrobenzoate (535 mg) as a bright yellow solid.

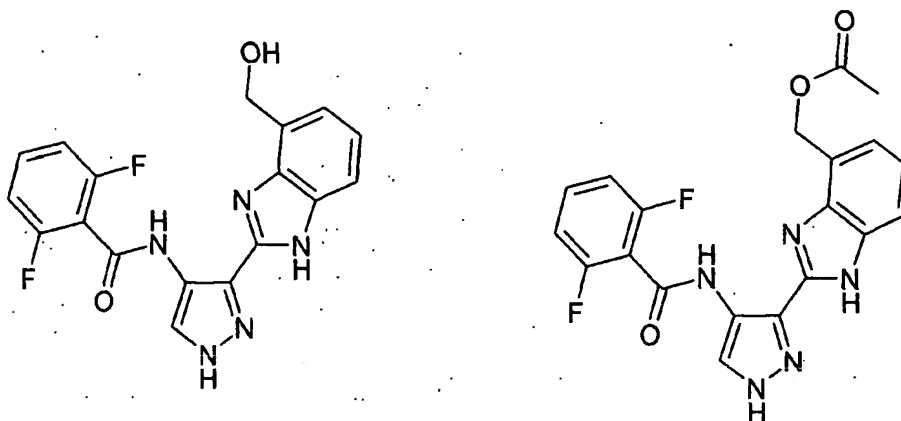
A mixture of methyl-2-amino-3-nitrobenzoate (530 mg) and 10% Pd/C (55 mg) in
 EtOH (10 mL) was stirred under an atmosphere of hydrogen at ambient temperature
 for 16 h. The catalyst was removed by filtration through Celite and the filtrate
 reduced *in vacuo* to give methyl 2,3-diaminobenzoate (420 mg) as a yellow/brown
 15 oil which solidified on standing.

A mixture of 4-(2,6-difluorobenzoylamino)-1H-pyrazole-3-carboxylic acid (690
 mg, 2.6 mmol) (Example 16), methyl 2,3-diaminobenzoate (415 mg, 2.6 mmol),
 EDC (590 mg, 3.1 mmol) and HOBt (415 mg, 3.1 mmol) in DMF (10 mL) was
 stirred at ambient temperature for 16 h and then reduced *in vacuo*. The residue was
 20 partitioned between EtOAc and brine and the organic portion dried (MgSO₄),
 filtered, reduced then crystallised from hot EtOH. The amide intermediate (480 mg)
 was dissolved in AcOH (10 mL) then heated at reflux for 3 h. The reaction mixture

was reduced *in vacuo* and then azeotroped with toluene (2 x 20 mL) to afford 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester (420 mg) as a fawn coloured solid. (LC/MS: R_t 3.82, $[M+H]^+$ 398).

5 EXAMPLE 11

Synthesis of 2,6-Difluoro-N-[3-(4-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide, and Acetic acid 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazol-4-ylmethyl ester



10

A solution of methyl-2-(acetylamino)-3-nitrobenzoate (2.6 g) in EtOH (50 mL) was treated with concentrated hydrochloric acid (10 mL) then heated at reflux for 16 h. The reaction mixture was cooled, reduced *in vacuo* and azeotroped with toluene (2 x 50 mL) to give 2-amino-3-nitrobenzoic acid (1.83 g) as a bright yellow solid.

- 15 To a solution of 2-amino-3-nitrobenzoic acid (1.82 g, 10.0 mmol) in anhydrous THF (50 mL) was added sodium borohydride (770 mg, 20.0 mmol) followed by boron trifluoride diethyl etherate (2.5 mL, 20 mmol) and the mixture stirred at ambient temperature under a nitrogen atmosphere for 2 h. MeOH was cautiously added until gas evolution had ceased and the mixture reduced *in vacuo*. The residue
- 20 was partitioned between EtOAc and brine and the organic portion dried ($MgSO_4$) and reduced *in vacuo* to give 2-amino-3-nitrobenzyl alcohol (1.42 g) as a yellow solid.

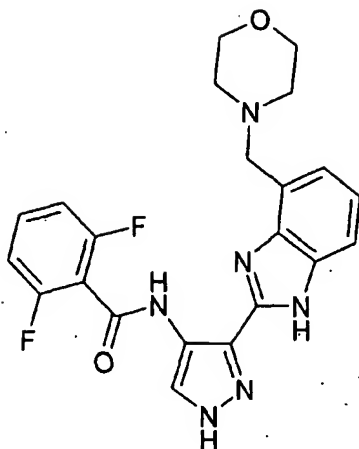
A mixture of 2-amino-3-nitrobenzyl alcohol (1.4 g) and 10% Pd/C (140 mg) in EtOH (40 mL) and DMF (10 mL) was stirred under an atmosphere of hydrogen at ambient temperature for 18 h. The catalyst was removed by filtration through Celite, the filtrate reduced *in vacuo* and azeotroped with toluene (2 x 50 mL) to give
 5 2,3-diaminobenzyl alcohol (1.15 g) as a dark brown solid.

A mixture of 4-(2,6-difluorobenzoylamino)-1H-pyrazole-3-carboxylic acid (1.0 g, 3.7 mmol) (Example 16), 2,3-diaminobenzylalcohol (560 mg, 4.1 mmol), EDC (870 mg, 4.5 mmol) and HOBt (610 mg, 4.5 mmol) in DMF (20 mL) was stirred at ambient temperature for 18 h and then reduced *in vacuo*. The residue was
 10 partitioned between EtOAc and brine and the organic portion dried (MgSO₄) and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO₂, EtOAc-hexane (1:1, 2:1)] to give 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (2-amino-3-hydroxymethyl-phenyl)-amide (860 mg).

4-(2,6-Difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (2-amino-3-hydroxymethyl-phenyl)-amide (100 mg, 0.26 mmol) was dissolved in AcOH (10 mL) then heated for 10 min at 150 °C (100 W) in a CEM discover microwave synthesiser. The reaction mixture was reduced then azeotroped with toluene (2 x 20 mL). The residue was purified by flash column chromatography [SiO₂, EtOAc-hexane (1:1, 2:1, 3:1)] to give 2,6-difluoro-N-[3-(4-hydroxymethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (25 mg) as an off white solid
 20 (LC/MS: R_t 2.70, [M+H]⁺ 370) and acetic acid 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzimidazol-4-ylmethyl ester (20 mg) as an off white solid. (LC/MS: R_t 3.60, [M+H]⁺ 412).

EXAMPLE 12

25 Synthesis of 2,6-Difluoro-N-[3-(4-morpholin-4-yl-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



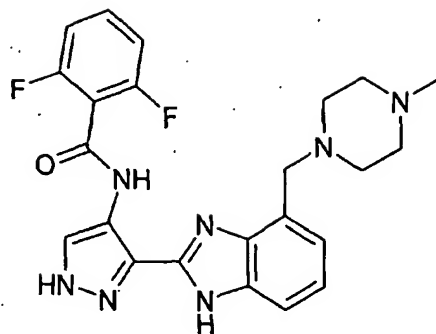
A mixture of 2,6-difluoro-N-[3-(4-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (200 mg, 0.54 mmol) and MnO_2 (500 mg) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (5:1, 12 mL) was stirred at ambient temperature for 18 h, then filtered
 5 through Celite and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2 , EtOAc-hexane (1:3, 1:2)] to give 2,6-difluoro-N-[3-(4-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (30 mg) as a cream solid.

To a solution of 2,6-difluoro-N-[3-(4-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (30 mg, 0.08 mmol) and morpholine (14 mg, 0.16 mmol) in
 10 CH_2Cl_2 (5 mL) and THF (2 mL) was added 3 Å molecular sieves (1 g) followed by sodium triacetoxyborohydride (50 mg, 0.24 mmol) and the mixture stirred at ambient temperature under a nitrogen atmosphere for 2 h. The reaction mixture was filtered through Celite, reduced *in vacuo* then purified by flash column
 15 chromatography [SiO_2 , EtOAc-hexane (1:1, 1:0), then CH_2Cl_2 -MeOH (95:5)] affording 2,6-difluoro-N-[3-(4-morpholin-4-yl-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (13 mg) as a cream solid. (LC/MS: R_t 1.80, $[\text{M}+\text{H}]^+$ 439).

EXAMPLE 13

Synthesis of 2,6-Difluoro-N-[3-(N-methyl-piperazinyl-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

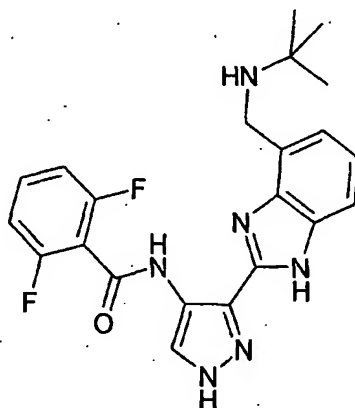
20



The compound was prepared in a manner analogous to Example 12, but using N-methylpiperazine in place of morpholine. (LC/MS: R_t 1.93, $[M+H]^+$ 452).

EXAMPLE 14

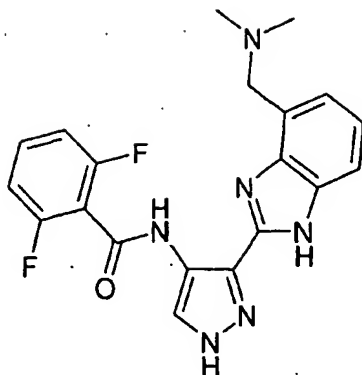
- 5 Synthesis of N-{3-[4-(*tert*-Butylamino-methyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-2,6-difluoro-benzamide



The compound was prepared in a manner analogous to Example 12, but using *tert*-butylamine in place of morpholine. (LC/MS: R_t 2.04, $[M+H]^+$ 425).

10 EXAMPLE 15

- Synthesis of N-[3-(4-Dimethylaminomethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide

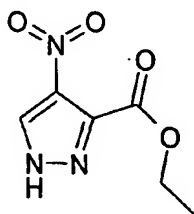


The compound was prepared in a manner analogous to Example 12, but using 35% dimethylamine in EtOH in place of morpholine. (LC/MS: R_t 1.85, $[M+H]^+$ 397).

EXAMPLE 16

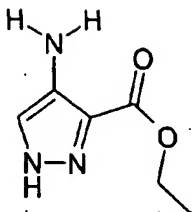
- 5 Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester

Step 1: Synthesis of 4-Nitro-1H-pyrazole-3-carboxylic acid ethyl ester



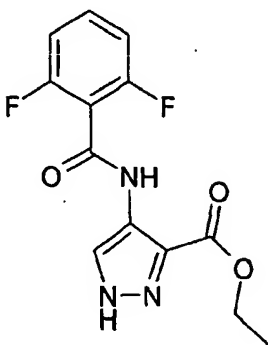
- 10 Thionyl chloride (2.90 mL, 39.8 mmol) was slowly added to a mixture of 4-nitro-3-pyrazolecarboxylic acid (5.68 g, 36.2 mmol) in EtOH (100 mL) at ambient temperature and the mixture stirred for 48 h. The mixture was reduced *in vacuo* and dried through azeotrope with toluene to afford 4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester as a white solid (6.42 g, 96%). (^1H NMR (400 MHz, DMSO- d_6) δ 14.4 (s, 1H), 9.0 (s, 1H), 4.4 (q, 2H), 1.3 (t, 3H)).

- 15 Step 2: Synthesis of 4-Amino-1H-pyrazole-3-carboxylic acid ethyl ester



A mixture of 4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester (6.40 g, 34.6 mmol) and 10% Pd/C (650 mg) in EtOH (150ml) was stirred under an atmosphere of hydrogen for 20 h. The mixture was filtered through a plug of Celite, reduced *in vacuo* and dried through azeotrope with toluene to afford 4-amino-1H-pyrazole-3-carboxylic acid ethyl ester as a pink solid (5.28 g, 98%). (¹H NMR (400 MHz, DMSO-d₆) δ 12.7 (s, 1H), 7.1 (s, 1H), 4.8 (s, 2H), 4.3 (q, 2H), 1.3 (t, 3H)).

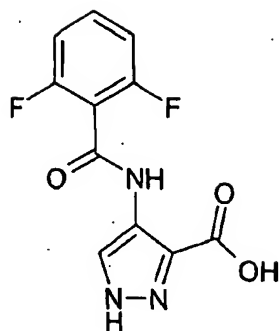
Step 3: Synthesis of 4-(2,6-Difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid ethyl ester



10

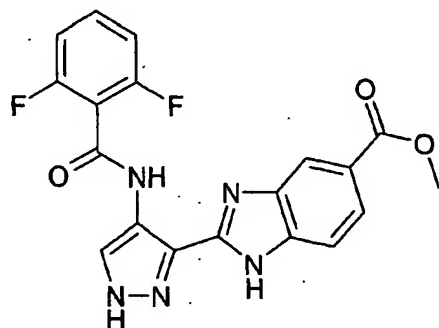
A mixture of 2,6-difluorobenzoic acid (6.32 g, 40.0 mmol), 4-amino-1H-pyrazole-3-carboxylic acid ethyl ester (5.96 g, 38.4 mmol), EDC (8.83 g, 46.1 mmol) and HOBt (6.23 g, 46.1 mmol) in DMF (100 mL) was stirred at ambient temperature for 6 h. The mixture was reduced *in vacuo*, water added and the solid formed collected by filtration and air-dried to give 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid ethyl ester as the major component of a mixture (15.3 g). (LC/MS: R_t 3.11, [M+H]⁺ 295.99).

Step 4: Synthesis of 4-(2,6-Difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid



A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid ethyl ester (10.2 g) in 2 M aqueous NaOH/MeOH (1:1, 250 mL) was stirred at ambient temperature for 14 h. Volatile materials were removed *in vacuo*, water (300 mL) added and the mixture taken to pH 5 using 1M aqueous HCl. The resultant precipitate was collected by filtration and dried through azeotrope with toluene to afford 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid as a pink solid (5.70 g). (LC/MS: R_t 2.33, $[M+H]^+$ 267.96).

Step 5: Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester



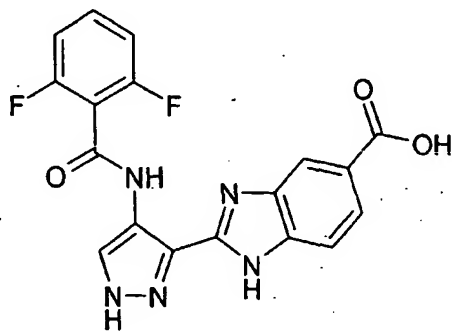
A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (500 mg, 1.87 mmol), methyl 3,4-diaminobenzoate (375 mg, 2.25 mmol), EDC (430 mg, 2.25 mmol) and HOBt (305 mg, 2.25 mmol) in DMF (5 mL) was stirred at ambient temperature for 12 h. The residue was reduced *in vacuo* and then dissolved in the minimum amount of methanol and petroleum ether added to give the intermediate

amide as a pink solid which was collected by filtration (427 mg). (LC/MS: R_t 3.24, $[M+H]^+$ 416.02).

A mixture of the amide (150 mg, 0.36 mmol) in glacial AcOH (4 mL) was heated in the microwave (100 W) at 120 °C for 10 mins. The mixture was reduced *in vacuo* and petroleum ether (3 mL) and methanol (2 mL) added forming a precipitate, which was collected by filtration to give 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (96 mg, 67%) as a pink solid. (LC/MS: R_t 3.67, $[M+H]^+$ 397.99).

EXAMPLE 17

10 Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid

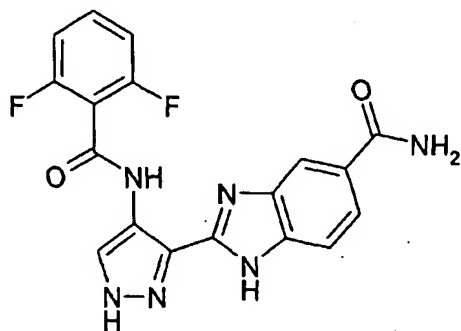


A mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (12.0 mg, 0.03 mmol) in 2 M aqueous NaOH/MeOH (1:1, 4 mL) was stirred at ambient temperature for 14 h. The mixture was reduced *in vacuo*, water (5 mL) added and the mixture taken to pH 4 using 1 M aqueous HCl. The precipitate formed was collected by filtration and dried under vacuum to give 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid as a pale coloured solid (6 mg, 52%).

20 (LC/MS: R_t 2.88, $[M+H]^+$ 383.97).

EXAMPLE 18

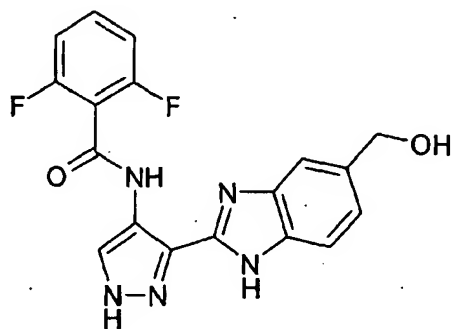
Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid amide



To a mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid (100 mg, 0.26 mmol), EDC (75 mg, 0.39 mmol) and HOBt (53 mg, 0.39 mmol) in DMF (1.5 mL) was successively added diisopropylethylamine (0.15 mL, 1.04 mmol) and ammonium chloride (28 mg, 0.52 mmol). The mixture was stirred at ambient temperature for 48 h and then reduced *in vacuo*. Water was added and the precipitate formed collected by filtration and dried through azeotrope with toluene to afford 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid amide (49 mg, 49%) as beige solid. (LC/MS: R_t 2.54, [M+H]⁺ 382.99).

EXAMPLE 19

Synthesis of 2,6-Difluoro-N-[3-(5-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

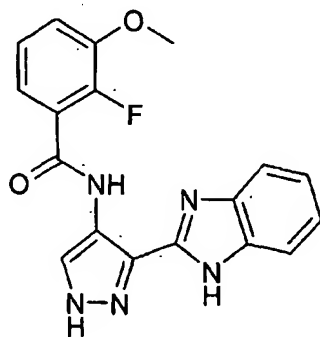


A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (584 mg, 2.19 mmol), (3,4-diamino-phenyl)-methanol (332 mg, 2.40 mmol), EDC (504 mg, 2.63 mmol) and HOBT (355 mg, 2.63 mmol) in DMF (15 mL) was stirred at ambient temperature for 20 h. The mixture was reduced *in vacuo* and the residue
 5 taken up in EtOAc, washed with water and brine and the organic portion dried (MgSO₄) and reduced *in vacuo* to give the intermediate amide (591 mg) as a brown solid. (LC/MS: R_t 2.34, [M+H]⁺ 388.00).

A mixture of the amide (575 mg) in glacial AcOH (4 mL) was heated in the microwave (80 W) at 90 °C for 20 min. The mixture was poured into water and the
 10 solid formed collected by filtration. The residue was taken up in MeOH (10 mL) and stirred in the presence of NaOMe (320 mg, 5.90 mmol) for 30 min. The mixture was reduced *in vacuo*, taken up in EtOAc and washed with water and brine, dried (MgSO₄) and reduced *in vacuo*. The residue was purified by column chromatography [SiO₂, EtOAc] to give 2,6-difluoro-N-[3-(5-hydroxymethyl-1H-
 15 benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide as a white solid (78 mg, 10% over two steps). (LC/MS: R_t 2.45, [M+H]⁺ 370.05).

EXAMPLE 20

Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-methoxybenzamide



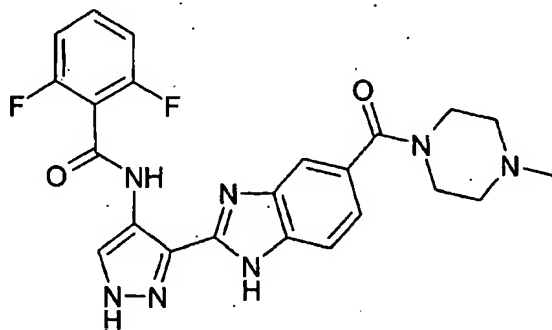
20

A mixture of 2-fluoro-3-methoxybenzoic acid (47 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBT (41 mg, 0.30 mmol) in DMF (1.5 mL) was stirred at ambient

temperature for 20 h. The reaction mixture was poured into water (30 mL) and the resultant solid collected by filtration and purified by re-crystallisation from MeOH/petrol to yield N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-methoxy-benzamide (7 mg, 8%) as a grey solid. (LC/MS: R_t 3.63, $[M+H]^+$ 352.00).

EXAMPLE 21

Synthesis of 2,6-Difluoro-N-{3-[5-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide

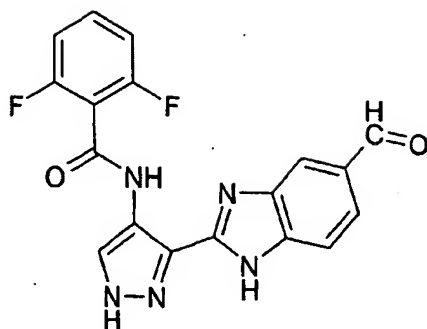


- 10 A mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid (115 mg, 0.30 mmol), 1-methyl-piperazine (50.0 μ L, 0.45 mmol), EDC (104 mg, 0.54 mmol) and HOBt (73.0 mg, 0.54 mmol) in DMF (5 mL) was stirred at ambient temperature for 14 h. The residue was reduced *in vacuo*, taken up in EtOAc and washed with water and brine, dried ($MgSO_4$) and
- 15 reduced *in vacuo* to give 2,6-difluoro-N-{3-[5-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (37 mg, 26%) as a pale yellow solid. (LC/MS: R_t 1.78, $[M+H]^+$ 466.09).

EXAMPLE 22

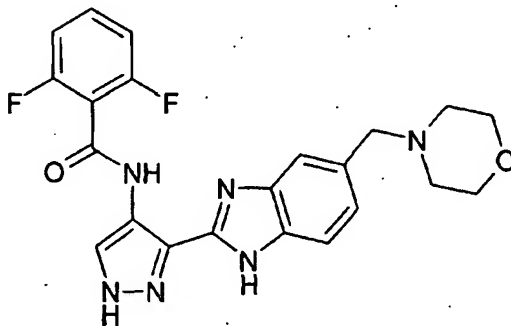
Synthesis of 2,6-Difluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

Step 1: Synthesis of 2,6-Difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



A mixture of 2,6-difluoro-N-[3-(5-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (800 mg, 2.17 mmol) and MnO_2 (5.00 g, 57.5 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1, 110 mL) was stirred at ambient temperature for 5 days. The mixture was filtered through a plug of Celite washing with MeOH and the filtrate reduced *in vacuo* to give 2,6-difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (380 mg, 48%) as a yellow solid. (LC/MS: R_t 3.41, $[\text{M}+\text{H}]^+$ 368.04).

Step 2: Synthesis of 2,6-Difluoro-N-[3-(5-morpholin-4-ylmethyl)-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

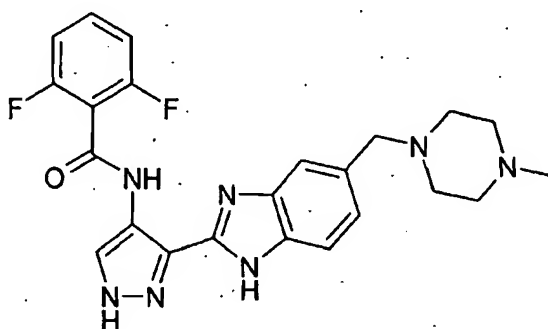


To a mixture of 2,6-difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (75.0 mg, 0.20 mmol) in anhydrous THF (5 mL) stirring at ambient temperature was successively added 3 Å molecular sieves, morpholine (35 μL , 0.40 mmol) and triacetoxy sodiumborohydride (127 mg, 0.60 mmol). The mixture was stirred for 4 h, MeOH (3 mL) added and then the mixture reduced *in*

vacuo. The residue was taken up in EtOAc, washed with water and brine, dried (MgSO₄), reduced *in vacuo* and then purified through preparative LC/MS to give 2,6-difluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (9 mg, 10%) as a white solid. (LC/MS: R_t 1.90, [M+H]⁺ 439.09).

5 EXAMPLE 23

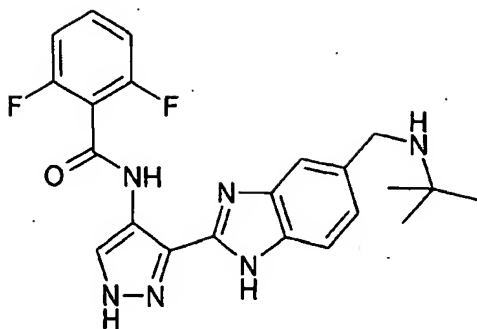
Synthesis of 2,6-Difluoro-N-{3-[5-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



The compound was prepared in a manner analogous to Example 22, however using 1-methyl piperazine (44.0 μ L, 0.40 mmol) as the amine fragment to give 2,6-difluoro-N-{3-[5-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (4 mg, 5%) as a yellow solid. (LC/MS: R_t 1.66, [M+H]⁺ 452.11)

EXAMPLE 24

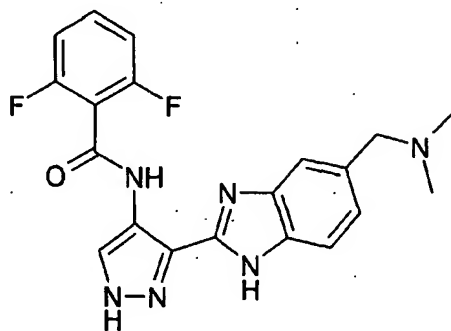
15 Synthesis of N-{3-[5-(*tert*-Butylamino-methyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-2,6-difluoro-benzamide



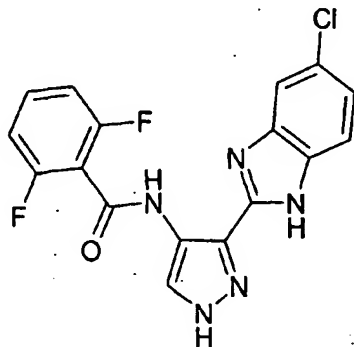
- The compound was prepared in a manner analogous to Example 22, however using *tert*-butylamine (42 μ L, 0.40 mmol) as the amine fragment to give N-[3-(5-(*tert*-butylamino-methyl)-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluorobenzamide (5 mg, 6%) as a white solid. (LC/MS: R_t 2.00, $[M+H]^+$ 425.11)

EXAMPLE 25

Synthesis of N-[3-(5-Dimethylaminomethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluorobenzamide

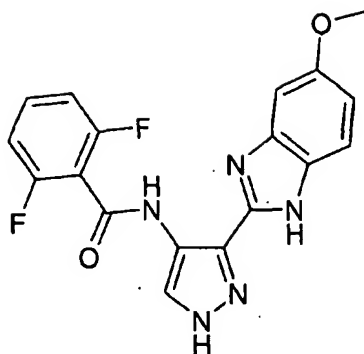


- The compound was prepared in a manner analogous to Example 22, however using 2,6-difluoro-N-[3-(5-formyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (57.4 mg, 0.16 mmol), dry THF (5 mL), 3Å molecular sieves, dimethylamine (35% in EtOH) (55 μ L, 0.31 mmol) and triacetoxy sodiumborohydride (100 mg, 0.47 mmol) to give N-[3-(5-dimethylaminomethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluorobenzamide (11 mg, 18%) as a yellow solid. (LC/MS: R_t 2.85, $[M+H]^+$ 397.17).

EXAMPLE 26**Synthesis of N-[3-(5-Chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide**

- 5 A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (50 mg, 0.18 mmol), 4-chlorophenylenediamine (30 mg, 0.21 mmol), EDC (45 mg, 0.22 mmol) and HOBt (30 mg, 0.22 mmol) in DMF (5 mL) was stirred at ambient temperature for 18 h. The reaction mixture was reduced *in vacuo* and the residue purified by column chromatography [SiO_2 , EtOAc/hexane (1:1)] to give the
- 10 intermediate amide. A mixture of the amide in AcOH (2 mL) was heated in a microwave (50W) at 140 °C for 15 min and then reduced *in vacuo*. The residue was purified by column chromatography [SiO_2 , EtOAc/petrol (1:1)] to give N-[3-(5-chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (20 mg) as a fawn solid. (LC/MS: R_t 4.16, $[\text{M}+\text{H}]^+$ 374).

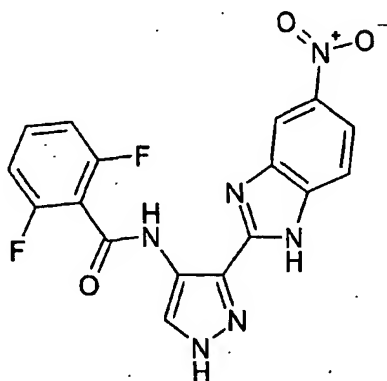
15 EXAMPLE 27**Synthesis of 2,6-Difluoro-N-[3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide**



- The compound was prepared in a manner analogous to Example 26, but using 4-methoxyphenylenediamine (28 mg, 0.21 mmol) as the amine fragment to give 2,6-difluoro-N-[3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (25 mg) as a pale brown solid. (LC/MS: R_t 3.26, $[M+H]^+$ 370).

EXAMPLE 28

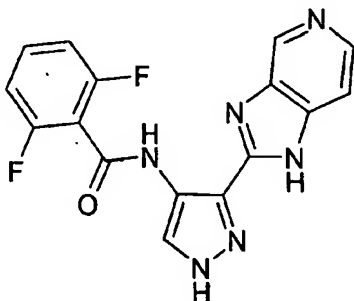
Synthesis of 2,6-Difluoro-N-[3-(5-nitro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



- 10 The compound was prepared in a manner analogous to Example 26, but using 4-nitrophenylenediamine (32 mg, 0.21 mmol) as the amine fragment to give 2,6-difluoro-N-[3-(5-nitro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (18 mg). (LC/MS: R_t 3.84, $[M+H]^+$ 385).

EXAMPLE 29

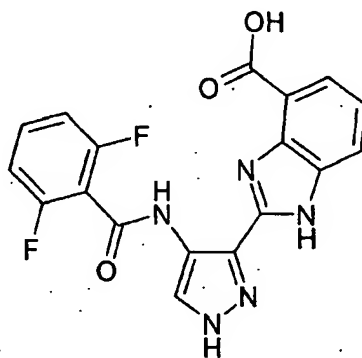
Synthesis of 2,6-Difluoro-N-[3-(1H-imidazo[4,5-c]pyridin-2-yl)-1H-pyrazol-4-yl]-benzamide



The compound was prepared in a manner analogous to Example 26, but using 3,4-diaminopyridine (22 mg, 0.21 mmol) as the amine fragment to give 2,6-difluoro-N-[3-(1H-imidazo[4,5-c]pyridin-2-yl)-1H-pyrazol-4-yl]-benzamide (13 mg) as a brown solid. (LC/MS: R_t 4.16, $[M+H]^+$ 341).

EXAMPLE 30

Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid

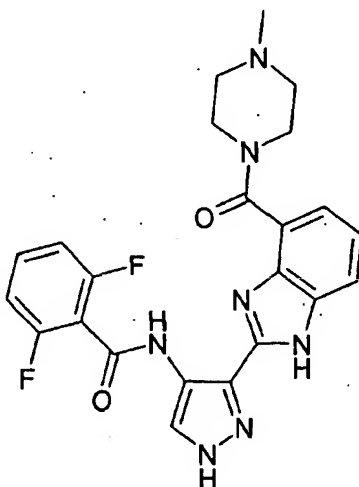


A solution of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester (220 mg, 0.55 mmol) in THF/water (1:1, 10 mL) was treated with lithium hydroxide hydrate (70 mg, 1.66 mmol) and

the mixture stirred at ambient temperature for 18 h. The volatiles were removed *in vacuo*, the mixture acidified to pH5 by the addition of 2M aqueous hydrochloric acid and the solid formed collected by filtration, washed with water then dried under vacuum to give 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid (165 mg) as a brown solid. (LC/MS: R_t 3.28, $[M+H]^+$ 384).

EXAMPLE 31

Synthesis of 2,6-Difluoro-N-{3-[4-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



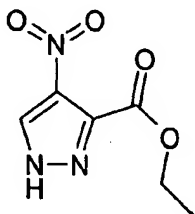
10

A mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid (50 mg, 0.13 mmol), N-methylpiperazine (20 μ l, 0.18mmol), EDC (30 mg, 0.15 mmol) and HOBt (22 mg, 0.15 mmol) in DMF (5 mL) was stirred at ambient temperature for 18 h. The mixture was reduced *in vacuo* and the residue purified by flash column chromatography [SiO_2 , CH_2Cl_2 /MeOH (95:5, 90:10)] to give 2,6-difluoro-N-{3-[4-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (14 mg) as a cream solid. (LC/MS: R_t 2.21, $[M+H]^+$ 466).

EXAMPLE 32

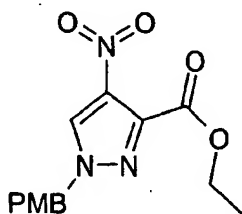
Synthesis of N-[3-(4-Phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-acetamide

Step 1: Synthesis of 4-Nitro-1H-pyrazole-3-carboxylic acid ethyl ester



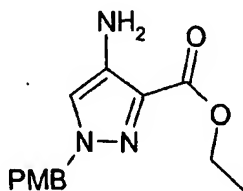
- Thionyl chloride (3.8 mL, 52.5 mmol) was added cautiously to a stirred, ice-cold mixture of 4-nitropyrazole-3-carboxylic acid (7.5 g, 47.7 mmol) in EtOH (150 mL), the mixture stirred at ambient temperature for 1 h then heated at reflux for 3 h. The reaction mixture was cooled, reduced *in vacuo* then azeotroped with toluene to give 4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester (8.8 g).

Step 2: Synthesis of 1-(4-methoxy-benzyl)-4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester



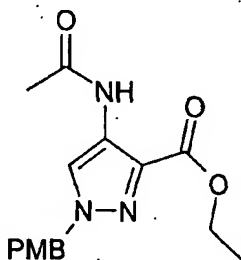
- To a solution of 4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester (8.8 g, 47.5 mmol) in MeCN (100 mL) was added K_2CO_3 (7.9 g, 57.0 mmol) followed by 4-methoxybenzyl chloride (7.1 mL, 52.3 mmol) and the mixture stirred at ambient temperature for 20 h. The mixture was reduced in *vacuo*, the residue partitioned between EtOAc and 2M aqueous hydrochloric acid and the organic portion washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and reduced in *vacuo*. The residue was purified by flash column chromatography [SiO_2 , EtOAc-hexane (1:4)] to give 1-(4-methoxy-benzyl)-4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester (11 g) as a colourless gum.

Step 3: Synthesis of 4-Amino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid ethyl ester



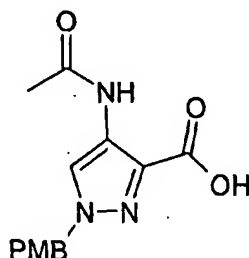
A mixture of 1-(4-methoxy-benzyl)-4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester (1 g) and 10% Pd/C (100 mg) in EtOH (10 mL) was stirred under an atmosphere of hydrogen at ambient temperature and pressure for 3 h. The catalyst was removed by filtration through Celite and the filtrate reduced *in vacuo* to give 4-amino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid ethyl ester (830 mg) as a purple gum.

Step 4: Synthesis of 4-Acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid ethyl ester



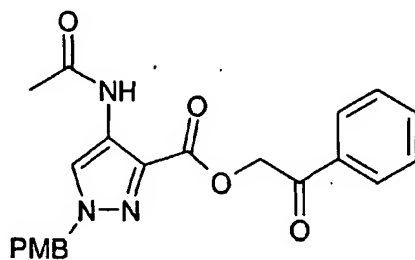
Acetic anhydride (1 mL) was added to a stirred solution of 4-amino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid ethyl ester (1 g) in pyridine (10 mL) and the mixture stirred at ambient temperature for 16 h. The reaction mixture was reduced *in vacuo*, the residue partitioned between EtOAc and 2M hydrochloric acid and the organic portion dried (MgSO₄) and concentrated under reduced pressure to give 4-acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid ethyl ester (1.2 g) as a pink solid.

Step 5: Synthesis of 4-Acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid



- A mixture of 4-acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid ethyl ester (470 mg, 1.5 mmol) in THF/water (1:1, 20 mL) was treated with lithium hydroxide monohydrate (70 mg, 1.6 mmol) and stirred at ambient temperature for 16 h. The volatiles were removed *in vacuo* and the remaining aqueous solution extracted with Et₂O. The aqueous layer was acidified with 2M hydrochloric acid, then extracted with EtOAc (2 x 20ml). The combined EtOAc layers were dried (MgSO₄) and reduced *in vacuo* to give 4-acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid (370 mg) as a white solid.

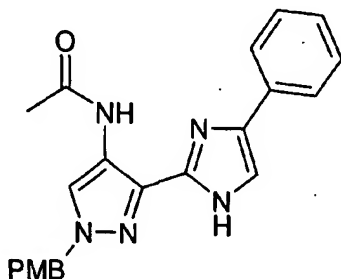
Step 6: Synthesis of 4-Acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid 2-oxo-2-phenyl-ethyl ester



- To a stirred solution of 4-acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid (300 mg, 0.95 mmol) in EtOH/water (1:1, 10 mL) was added cesium carbonate (190 mg, 0.57 mmol) followed by 2-bromoacetophenone (210 mg, 1.04 mmol) and the mixture stirred at 80°C for 3 h. The reaction mixture was allowed to cool to ambient temperature and the solid formed collected by filtration,

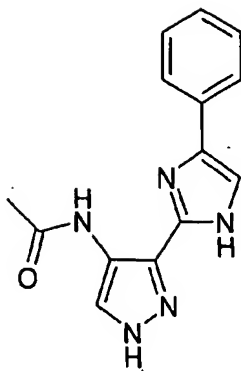
washed with EtOH/water (1:1, 5 mL) then dried under vacuum to give 4-acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid 2-oxo-2-phenyl-ethyl ester (330 mg) as a white solid.

Step 7: Synthesis of N-[1-(4-Methoxy-benzyl)-3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-acetamide



A mixture of 4-acetylamino-1-(4-methoxy-benzyl)-1H-pyrazole-3-carboxylic acid 2-oxo-2-phenyl-ethyl ester (100 mg, 0.24 mmol) and ammonium acetate (380 mg, 4.9 mmol) in *p*-xylene (5 mL) was heated at 200°C (100W) for 20 min in a CEM discover microwave synthesiser. The reaction mixture was reduced, the residue partitioned between EtOAc and brine and the organic portion dried (MgSO₄) and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO₂, EtOAc/hexane (1:2, 1:1)] to give N-[1-(4-methoxy-benzyl)-3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-acetamide (25 mg) as a cream solid. (LC/MS: R_t 3.45, [M+H]⁺ 388).

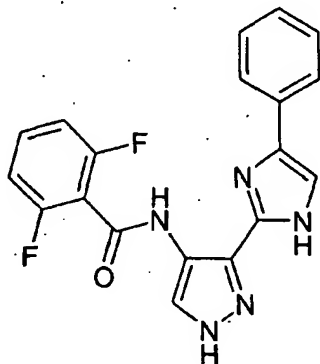
Step 8: Synthesis of N-[3-(4-Phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-acetamide



A mixture of N-[1-(4-methoxy-benzyl)-3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-acetamide (20 mg) and anisole (20 μ L) in trifluoroacetic acid (1 mL) was heated at 120°C (50W) for 15 min in a CEM discover microwave synthesiser. The reaction mixture was reduced then azeotroped with toluene (2 x 10 mL). The residue was purified by flash column chromatography [SiO₂, EtOAc/hexane (1:1, 1:0)] to give N-[3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-acetamide (10 mg) as an off-white solid. (LC/MS: R_t 1.94, [M+H]⁺ 268).

EXAMPLE 33

10 Synthesis of 2,6-Difluoro-N-[3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



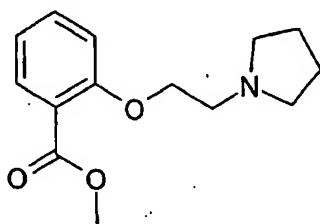
The compound was prepared in a manner analogous to Example 32, but using 2,6-difluorobenzoic acid, EDC and HOBt in place of acetic anhydride and pyridine in

step 4, to give 2,6-difluoro-N-[3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (25 mg) as a cream solid. (LC/MS: R_t 3.52, $[M+H]^+$ 366).

EXAMPLE 34

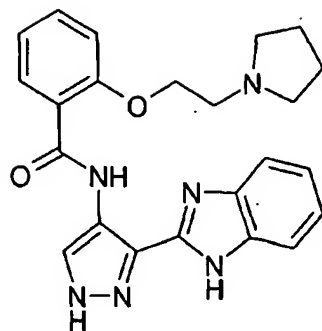
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-pyrrolidin-1-yl-ethoxy)-benzamide

Step 1: Synthesis of 2-(2-Pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester



To a mixture of triphenylphosphine (0.79 g, 3.0 mmol) in THF (15 mL) was successively added diisopropylazodicarboxylate (0.61 g, 3.0 mmol) followed by methyl salicylate (0.46 g, 3.0 mmol) and the resultant mixture stirred at ambient temperature for 1 h. 1-(2-Hydroxyethyl)-pyrrolidine (0.35 g, 3.0 mmol) was then added drop-wise and the reaction mixture left stirring at ambient temperature for a further 5 h. The reaction mixture was reduced *in vacuo* and purified by flash column chromatography [SiO_2 , EtOAc/MeOH (3:1, 1:1)] to give 2-(2-pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester as a clear yellow oil (446 mg, 60 %). (LC/MS: R_t 1.58, $[M+H]^+$ 250.05).

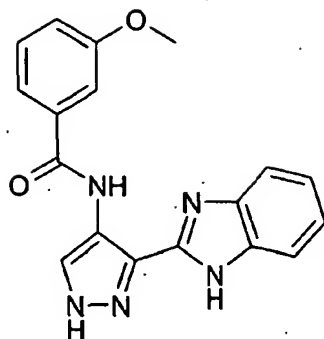
Step 2: Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-pyrrolidin-1-yl-ethoxy)-benzamide



2-(2-Pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester (125 mg, 0.50 mmol) and lithium hydroxide (21 mg, 0.50 mmol) were dissolved in THF/H₂O (1:1, 2 mL) and the mixture stirred at ambient temperature for 20 h. The reaction mixture was
 5 reduced *in vacuo* and azeotroped with toluene (3 x 5 mL) to give a white solid, which was dissolved in water (1 mL) and acidified with 2 M aqueous HCl (1 mL). The resulting solution was reduced *in vacuo* and azeotroped with toluene (3 x 5 mL) to give a pale yellow gel, which was combined with 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100 mg, 0.50 mmol), EDC (116 mg, 0.60 mmol) and
 10 HOBt (81 mg, 0.60 mmol) and stirred at ambient temperature in DMF (3 mL) for 20 h. The reaction mixture was reduced *in vacuo* and purified by flash column chromatography [SiO₂, CH₂Cl₂/MeOH (95:5, 87.5:12.5) then 120 DMAW] to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-pyrrolidin-1-yl-ethoxy)-benzamide (63 mg, 30%) as a pale pink solid. (LC/MS: R_t 2.08, [M+H]⁺ 417.11).

15 EXAMPLE 35

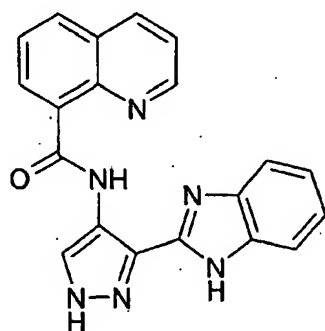
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-methoxybenzamide



A mixture of 3-methoxybenzoic acid (84 mg, 0.55 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100 mg, 0.50 mmol), EDC (116 mg, 0.60 mmol) and HOBt (81 mg, 0.60 mmol) was stirred at ambient temperature in DMSO (3 mL) for 20 h. The reaction mixture was poured into water (30 mL) and the resultant solid was collected by filtration and purified by flash column chromatography [SiO₂, 120 DMAW] to yield N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-methoxybenzamide as a pale pink-grey solid (21 mg, 13 %). (LC/MS: R_t 3.81, [M+H]⁺ 334.03).

10 EXAMPLE 36

Synthesis of Quinoline-8-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

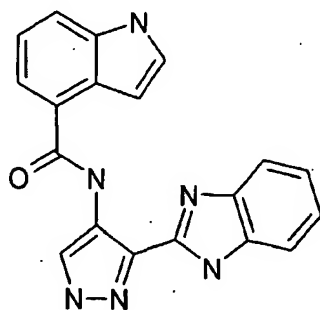


A mixture of quinoline-8-carboxylic acid (104 mg, 0.60 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100 mg, 0.50 mmol), EDC (116 mg, 0.60 mmol) and HOBt (81 mg, 0.60 mmol) was stirred at room temperature in

DMF (1.5 mL) for 20 h. The reaction mixture was purified by preparative LC/MS to give quinoline-8-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (11 mg, 6%) as a brown solid. (LC/MS: R_t 3.85, $[M+H]^+$ 355.11).

EXAMPLE 37

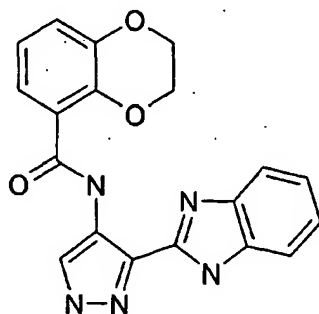
5 Synthesis of 1H-Indole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



The compound was prepared in a manner analogous to AT5469, however using indole-4-carboxylic acid to give 1H-indole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (16 mg) as a pale brown solid. (LC/MS: R_t 3.28, $[M+H]^+$ 343.07)

EXAMPLE 38

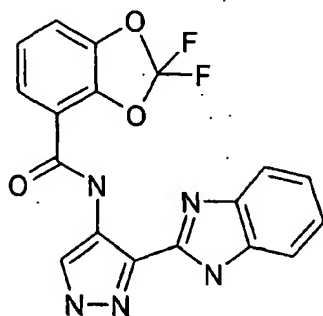
10 Synthesis of 2,3-Dihydro-benzo[1,4]dioxine-5-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



The compound was prepared in a manner analogous to AT5469, however using 4-benzodioxane-5-carboxylic acid to give 2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (30 mg) as an off-white solid. (LC/MS: R_t 3.54, $[M+H]^+$ 362.07).

5 **EXAMPLE 39**

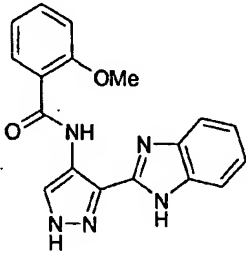
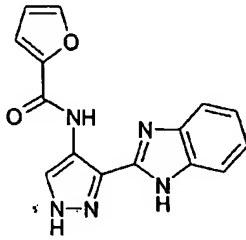
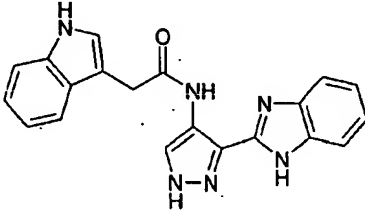
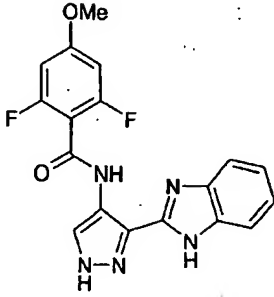
Synthesis of 2,2-Difluoro-benzo[1,3]dioxole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

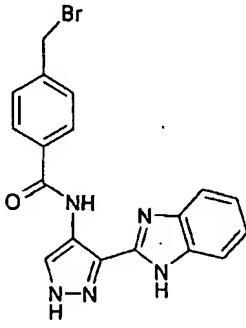
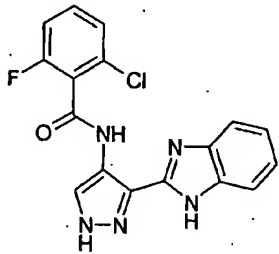
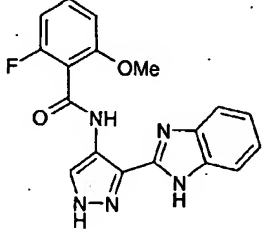
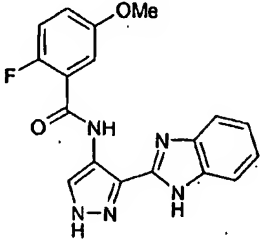


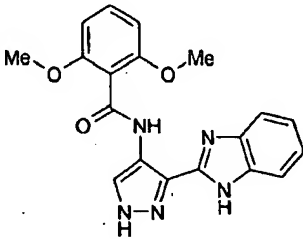
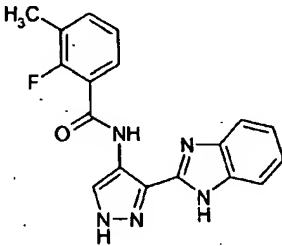
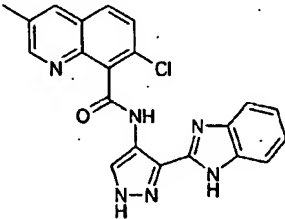
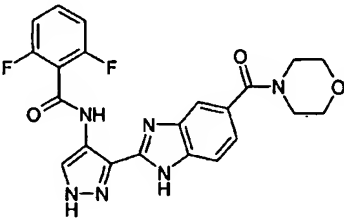
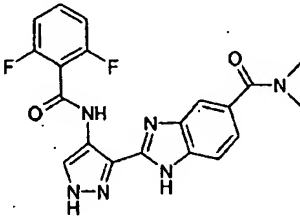
10 The compound was prepared in a manner analogous to Example 36, however using 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid to give 2,2-difluoro-benzo[1,3]dioxole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (24 mg) as an off-white solid. (LC/MS: R_t 4.26, $[M+H]^+$ 384.04).

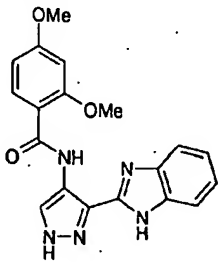
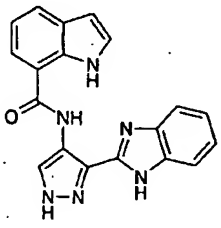
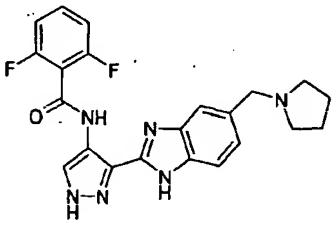
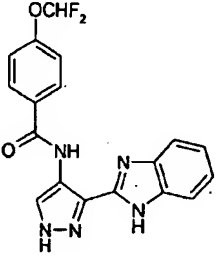
EXAMPLES 40 – 57

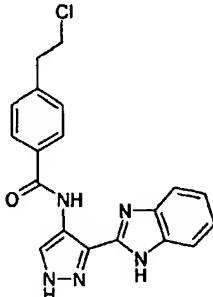
15 By following the procedures described in the above examples, or procedures analogous thereto, the following compounds were prepared.

Example No.	Compound
40	 <chem>COc1ccccc1C(=O)Nc2c[nH]c3c2c[nH]c4ccccc34</chem>
41	 <chem>c1ccoc1C(=O)Nc2c[nH]c3c2c[nH]c4ccccc34</chem>
42	 <chem>c1ccc2c(c1)c[nH]c2CC(=O)Nc3c[nH]c4c3c[nH]c5ccccc45</chem>
43	 <chem>COc1cc(F)c(F)cc1C(=O)Nc2c[nH]c3c2c[nH]c4ccccc34</chem>

Example No.	Compound
44	 <chem>BrCc1ccc(cc1)C(=O)Nc2nc3c[nH]n3n2</chem>
45	 <chem>Fc1cc(Cl)ccc1C(=O)Nc2nc3c[nH]n3n2</chem>
46	 <chem>COc1cc(F)ccc1C(=O)Nc2nc3c[nH]n3n2</chem>
47	 <chem>Fc1cccc(c1)C(=O)Nc2nc3c[nH]n3n2</chem>

Example No.	Compound
48	 <chem>COc1cc(OC)c(C(=O)Nc2c[nH]c3c2n[nH]c4ccccc34)cc1</chem>
49	 <chem>CC1=CC(=C(C=C1)F)C(=O)Nc2c[nH]c3c2n[nH]c4ccccc34</chem>
50	 <chem>CC1=CC=C2C(=C1)N=CC=C2C(=O)Nc3c[nH]c4c3n[nH]c5ccccc45</chem>
51	 <chem>CN1CCOCC1C(=O)c2ccc3c2n[nH]c4c3c[nH]c5c4c[nH]c6cc(F)c(C(=O)N)cc6F</chem>
52	 <chem>CN(C)C(=O)c1ccc2c1n[nH]c3c2c[nH]c4c3c[nH]c5c4c[nH]c6cc(F)c(C(=O)N)cc6F</chem>

Example No.	Compound
53	 <chem>COc1cc(OC)cc(C(=O)Nc2c[nH]n2-c3c[nH]c4ccccc34)c1</chem>
54	 <chem>c1ccc2c(c1)c[nH]2C(=N1C=NC=C1C(=O)N)N</chem>
55	 <chem>Fc1cc(F)cc(C(=O)Nc2c[nH]n2-c3c[nH]c4cc(ccc34)CC5CCCN5)c1</chem>
56	 <chem>COc1ccc(C(=O)Nc2c[nH]n2-c3c[nH]c4ccccc34)cc1F</chem>

Example No.	Compound
57	

BIOLOGICAL ACTIVITY

EXAMPLE 58

5 Measurement of CDK2 Kinase Inhibitory Activity (IC₅₀)

Compounds of the invention were tested for kinase inhibitory activity using the following protocol.

- 1:7 μ l of active CDK2/CyclinA (Upstate Biotechnology, 10U/ μ l) is diluted in assay buffer (250 μ l of 10X strength assay buffer (200mM MOPS pH 7.2, 250mM β -glycerophosphate, 50mM EDTA, 150mM MgCl₂), 11.27 μ l 10mM ATP, 2.5 μ l 1M DTT, 25 μ l 100mM sodium orthovanadate, 708.53 μ l H₂O), and 10 μ l mixed with 10 μ l of histone substrate mix (60 μ l bovine histone H1 (Upstate Biotechnology, 5 mg/ml), 940 μ l H₂O, 35 μ Ci γ ³³P-ATP) and added to 96 well plates along with 5 μ l of various dilutions of the test compound in DMSO (up to 15 2.5%). The reaction is allowed to proceed for 5 hours before being stopped with an excess of ortho-phosphoric acid (30 μ l at 2%).

- γ ³³P-ATP which remains unincorporated into the histone H1 is separated from phosphorylated histone H1 on a Millipore MAPH filter plate. The wells of the MAPH plate are wetted with 0.5% orthophosphoric acid, and then the results of the reaction are filtered with a Millipore vacuum filtration unit through the wells. 20 Following filtration, the residue is washed twice with 200 μ l of 0.5%

orthophosphoric acid. Once the filters have dried, 25 μ l of Microscint 20 scintillant is added, and then counted on a Packard Topcount for 30 seconds.

The % inhibition of the CDK2 activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the CDK2 activity (IC_{50}).

The compounds of Examples 3 to 57 each have IC_{50} values of less than 20 μ M or provide at least 50% inhibition of the CDK2 activity at a concentration of 10 μ M. Preferred compounds have IC_{50} values of less than 1 μ M.

EXAMPLE 59

10 CDK Selectivity Assays

Compounds of the invention were tested for kinase inhibitory activity against a number of different kinases using the general protocol described in Example 40, but modified as set out below.

Kinases are diluted to a 10x working stock in 20mM MOPS pH 7.0, 1mM EDTA, 0.1% γ -mercaptoethanol, 0.01% Brij-35, 5% glycerol, 1mg/ml BSA. One unit equals the incorporation of 1nmol of phosphate per minute into 0.1mg/ml histone H1, or CDK7 substrate peptide at 30 $^{\circ}$ C with a final ATP concentration of 100uM.

The substrate for all the CDK assays (except CDK7) is histone H1, diluted to 10X working stock in 20mM MOPS pH 7.4 prior to use. The substrate for CDK7 is a specific peptide diluted to 10X working stock in deionised water.

Assay Procedure for CDK1/cyclinB, CDK2/cyclinA, CDK2/cyclinE, CDK3/cyclinE, CDK5/p35, CDK6/cyclinD3:

In a final reaction volume of 25 μ l, the enzyme (5-10mU) is incubated with 8mM MOPS pH 7.0, 0.2mM EDTA, 0.1mg/ml histone H1, 10mM MgAcetate and [γ - 33 P-ATP] (specific activity approx 500cpm/pmol, concentration as required). The reaction is initiated by the addition of Mg^{2+} [γ - 33 P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5 μ l of a 3%

phosphoric acid solution. 10ml of the reaction is spotted onto a P30 filter mat and washed 3 times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and counting.

Assay procedure for CDK7/cyclinH/MAT1

- 5 In a final reaction volume of 25 μ l, the enzyme (5-10mU) is incubated with 8mM MOPS pH 7.0, 0.2mM EDTA, 500 μ M peptide, 10mM MgAcetate and [γ -³³P-ATP] (specific activity approx 500cpm/pmol, concentration as required). The reaction is initiated by the addition of Mg²⁺+ [γ -³³P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10ml of the reaction is spotted onto a P30 filtermat and washed 3 times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and counting.

The compounds of Examples 6, 12, 13, 14 and 21 have IC50 values of < 1 μ M against CDK 1, 3, 5, 6 and 7.

15 EXAMPLE 60

Anti-proliferative Activity

- The anti-proliferative activities of compounds of the invention were determined by measuring the ability of the compounds to inhibition of cell growth in a number of cell lines. Inhibition of cell growth was measured using the Alamar Blue assay (Nociari, M. M, Shalev, A., Benias, P., Russo, C. *Journal of Immunological Methods* 1998, 213, 157-167). The method is based on the ability of viable cells to reduce resazurin to its fluorescent product resorufin. For each proliferation assay cells were plated onto 96 well plates and allowed to recover for 16 hours prior to the addition of inhibitor compounds for a further 72 hours. At the end of the incubation period 10% (v/v) Alamar Blue was added and incubated for a further 6 hours prior to determination of fluorescent product at 535nm ex / 590nm em. In the case of the non-proliferating cell assay cells were maintained at confluence for 96 hour prior to the addition of inhibitor compounds for a further 72 hours. The

number of viable cells was determined by Alamar Blue assay as before. All cell lines were obtained from ECACC (European Collection of cell Cultures).

By following the protocol set out above, compounds of the invention were found to inhibit cell growth in a number of cell lines.

5 EXAMPLE 61

Measurement of inhibitory activity against Glycogen Synthase Kinase-3 (GSK-3)

GSK3 β (human) is diluted to a 10x working stock in 50mM Tris pH 7.5, 0.1mM EGTA, 0.1mM sodium vanadate, 0.1% β -mercaptoethanol, 1mg/ml BSA. One unit equals the incorporation of 1nmol of phosphate per minute phospho-glycogen
10 synthase peptide 2 per minute.

In a final reaction volume of 25 μ l, GSK3 β (5-10 mU) is incubated with 8mM MOPS 7.0, 0.2mM EDTA, 20 μ M YRRAAVPPSPSLSRHSSPHQS(p)EDEEE (phospho GS2 peptide), 10mM MgAcetate and [γ -³³P-ATP] (specific activity approx 500cpm/pmol, concentration as required). The reaction is initiated by the
15 addition of Mg²⁺+ [γ -³³P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is spotted onto a P30 filter mat and washed 3 times for 5 minutes in 50mM phosphoric acid and once in methanol prior to drying and counting.

20 The compounds of Examples 6 and 12 have IC₅₀ values of < 1 μ M against GSK3 β .

PHARMACEUTICAL FORMULATIONS

EXAMPLE 62

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by
25 mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

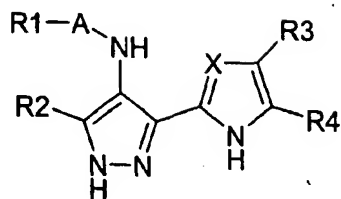
A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

5 Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and
10 illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the formula (I):



5

wherein

X is CR⁵ or N;

A is a bond or $-(CH_2)_m-(B)_n-$;

B is C=O, NR⁸(C=O) or O(C=O) wherein R⁸ is hydrogen or C₁₋₄ hydrocarbyl optionally substituted by hydroxy or C₁₋₄ alkoxy;

10

m is 0, 1 or 2;

n is 0 or 1;

R¹ is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C₁₋₈ hydrocarbyl group;

R² is hydrogen, halogen, methoxy, or a C₁₋₄ hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy;

15

R³ and R⁴ are the same or different and each is selected from hydrogen, optionally substituted C₁₋₈ hydrocarbyl and carbocyclic or heterocyclic groups having from 3 to 12 ring members;

or R³ and R⁴ together with the carbon atoms to which they are attached form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S; and

20

R⁵ is hydrogen, a group R² or a group R¹⁰ wherein R¹⁰ is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups

25

having from 3 to 12 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;

R^c is selected from hydrogen and C₁₋₄ hydrocarbyl; and

X¹ is O, S or NR^c and X² is =O, =S or =NR^c.

- 10 2. A compound according to claim 1 wherein X is N.
3. A compound according to claim 1 wherein X is CR⁵.
4. A compound according to claim 3 wherein R⁵ is a group R².
5. A compound according to claim 3 wherein R⁵ is a group R¹⁰.
6. A compound according to claim 1 wherein n is 0, X is N or CR⁵ and R⁵ is hydrogen or a group R¹⁰.
- 15 7. A compound according to claim 1 wherein n is 1, X is N or CR⁵ and R⁵ is hydrogen or a group R².
8. A compound according to claim 1 wherein m is 0 or 1, n is 1 and B is C=O.
9. A compound according to claim wherein m is 0, n is 1 and B is C=O.
- 20 10. A compound according to any one of the preceding claims wherein R² is hydrogen, fluorine or methyl.
11. A compound according to claim 10 wherein R² is hydrogen.
12. A compound according to any one of the preceding claims wherein R³ and R⁴ together with the carbon atoms to which they are attached form a fused

carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S.

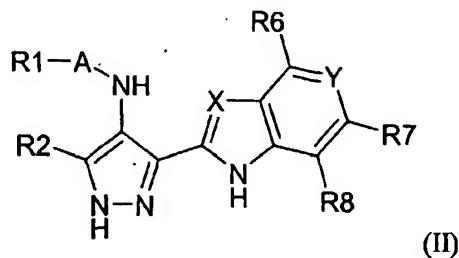
13. A compound according to claim 12 wherein the fused carbocyclic or heterocyclic ring is an aromatic ring.
- 5 14. A compound according to claim 13 wherein the fused aromatic ring is carbocyclic or contains a single heteroatom which is nitrogen.
15. A compound according to any one of claims 12 to 15 wherein the fused carbocyclic or heterocyclic ring has six ring members.
16. A compound according to claim 15 wherein the fused carbocyclic or
10 heterocyclic ring is a benzene ring.
17. A compound according to claim 12 wherein the fused carbocyclic or heterocyclic ring is substituted by up to 4 groups R^{10} .
18. A compound according to claim 12 wherein the substituents on the fused carbocyclic or heterocyclic ring are selected from halogen, hydroxy,
15 trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 7 (typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8}
20 hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c ,
25 $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c , X^1 and X^2 are as defined in claim 1.

19. A compound according to claim 18 wherein the groups on the fused carbocyclic or heterocyclic group formed by R^3 and R^4 are selected from halogen, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic group having 3-7 ring members and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, heterocyclic group with 3-7 ring members.
20. A compound according to any one of claims 1 to 19 wherein R^1 is a carbocyclic or heterocyclic group having from 3 to 12 ring members,
21. A compound according to claim 20 wherein the carbocyclic or heterocyclic group is monocyclic or bicyclic.
22. A compound according to claim 20 or 21 wherein the carbocyclic or heterocyclic group is an aryl or heteroaryl group.
23. A compound according to claim 22 wherein the aryl or heteroaryl group is selected from phenyl, indanyl, indenyl, tetrahydronaphthyl, pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.
24. A compound according to claim 23 wherein the aryl or heteroaryl group is selected from phenyl, furanyl, indolyl, oxazolyl, isoxazolyl, pyridyl,

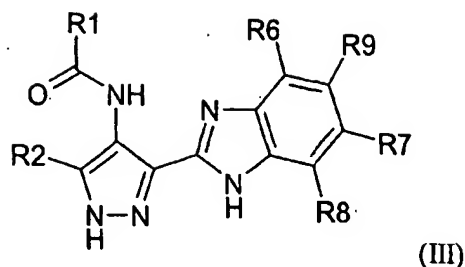
quinolinyl, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, imidazolyl and thiophenyl.

25. A compound according to claim 24 wherein the aryl or heteroaryl group is selected from furanyl, indolyl, oxazolyl, isoxazolyl, pyridyl, quinolinyl, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole.
26. A compound according to claim 25 wherein the aryl or heteroaryl group is selected from furanyl and 2,3-dihydro-benzo[1,4]dioxine groups.
27. A compound according to any one of claims 20 to 26 wherein R^1 is a carbocyclic or heterocyclic group unsubstituted or substituted by one or more substituent groups R^{10} as defined in claim 1.
28. A compound according to claim 27 wherein R^1 is unsubstituted or is substituted by one or more substituent groups selected from the group R^{10a} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $X^3C(X^4)$, $C(X^4)X^3$, $X^3C(X^4)X^3$, S, SO, or SO_2 , and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy; wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , $X^3C(X^4)$, $C(X^4)X^3$ or $X^3C(X^4)X^3$; X^3 is O or S; and X^4 is =O or =S.
29. A compound according to claim 28 wherein R^1 is unsubstituted.
30. A compound according to claim 28 wherein R^1 is substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, a group R^a-R^b wherein R^a is a bond or O, and R^b is selected from hydrogen and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxyl and halogen.

31. A compound according to any one of claims 27, 28 and 30 wherein R^1 is a five or six membered ring (e.g. a carbocyclic ring such as a phenyl ring), having 1, 2 or 3 substituents.
32. A compound according to claim 31 wherein R^1 is a phenyl group having 1, 2 or 3 substituents located at any one or more of the 2-, 3-, 4- or 6-positions around the phenyl ring.
33. A compound according to claim 32 wherein the phenyl group R^1 is 2,6-disubstituted, 2,3-disubstituted, 2,4-disubstituted 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted.
34. A compound according to claim 33 wherein the phenyl group R^1 is disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and R^a-R^b , where R^a is O and R^b is C_{1-4} alkyl.
35. A compound according to claim 1 having the formula (II):



- wherein R^1 , R^3 and X are as defined in any one of the preceding claims; Y is N or CR^9 wherein R^9 is hydrogen or a group R^{10} ; and R^6 , R^7 and R^8 are the same or different and each is hydrogen or a group R^{10} .
36. A compound according to claim 35 wherein X is N.
37. A compound according to claim 36 wherein R^6 is other than amino.
38. A compound according to claim 35 or claim 36 wherein Y is CR^9 .
39. A compound according to claim 1 having the formula (I):



40. A compound according to claim 39 wherein R^2 is hydrogen or C_{1-4} alkyl.
41. A compound according to claim 40 wherein R^2 is hydrogen.
- 5 42. A compound according to any one of claims 39 to 41 wherein R^1 is 2,3 disubstituted, 2,6 disubstituted or 2,4,6, trisubstituted phenyl or 2, 3-dihydro-benzo[1,4]dioxine, where the substituents are selected from halogen and C_{1-4} alkoxy.
- 10 43. A compound according to claim 42 wherein R^1 is selected from 2,6-difluorophenyl, 2-fluoro-6-methoxyphenyl, 2-chloro-6-fluorophenyl, 2,6-dichlorophenyl, 2,4,6-trifluorophenyl, 2,6-difluoro-4-methoxyphenyl, and 2,3-dihydro-benzo[1,4]dioxine.
44. A compound according to claim 43 wherein R^1 is 2,6-difluorophenyl.
- 15 45. A compound according to any one of claims 39 to 44 wherein R^6 to R^9 are each hydrogen or are selected from halogen (e.g. fluorine or chlorine), cyano, hydroxy, trifluoromethyl, nitro, a group R^a-R^b wherein R^a is a bond, O, CO or $C(X^2)X^1$ and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, more preferably 5 to 7 ring members, and a C_{1-8} hydrocarbyl group, more preferably a C_{1-4} hydrocarbyl group, optionally substituted by one or more substituents selected from hydroxy, 20 C_{1-4} acyloxy, mono- or di- C_{1-4} hydrocarbylamino, heterocyclic groups having from 3 to 12 ring members, more preferably 4 to 7 ring members; where R^c is selected from hydrogen and C_{1-4} hydrocarbyl, X^1 is O, NR^c and X^2 is =O.

46. A compound according to claim 45 wherein R^6 to R^9 are each hydrogen or a group R^a-R^b wherein R^a is a bond, CO, $C(X^2)X^1$ and R^b is selected from hydrogen, saturated heterocyclic groups having 5 or 6 ring members e.g. pyrrolidine, N-methyl piperazine or morpholine, and a C_{1-4} hydrocarbyl group, optionally substituted by one or more substituents selected from mono- or di- C_{1-4} hydrocarbylamino, saturated heterocyclic groups having from 6 ring members e.g. N-methyl piperazine or morpholine; where X^1 is NR^c , X^2 is $=O$ and R^c is selected from hydrogen and C_{1-4} hydrocarbyl.
47. A compound according to any one of claims 39 to 46 wherein at least one, more preferably at least two, and more typically at least three of R^6 to R^9 are hydrogen.
48. A compound according to claim 47 wherein one of R^6 to R^9 is a group R^{10} and the others are each hydrogen.
49. A compound according to claim 48 wherein R^6 is a substituent group R^{10} and R^7 to R^9 are each hydrogen, or R^9 is a substituent group R^{10} and R^6 to R^8 are each hydrogen.
50. A compound according to any one of the preceding claims in the form of a salt or solvate.
51. A compound of the formula (I) as defined in any one of claims 1 to 50 for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.
52. The use of a compound of the formula (I) as in any one of claims 1 to 50 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.
53. A method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises

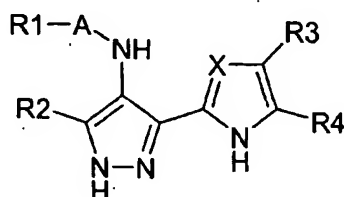
administering to a subject in need thereof a compound of the formula (I) as defined in any one of claims 1 to 50.

54. A method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined in any one of claims 1 to 50.
55. A method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound of the formula (I) as defined in any one of claims 1 to 50.
56. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 50 in an amount effective in inhibiting abnormal cell growth.
57. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 50 in an amount effective to inhibit cdk2 activity.
58. A compound of the formula (I) as defined in any one of claims 1 to 50 for use in the prophylaxis or treatment of a disease state or condition mediated by glycogen synthase kinase-3.
59. The use of a compound of the formula (I) as in any one of claims 1 to 50 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by glycogen synthase kinase-3.
60. A method for the prophylaxis or treatment of a disease state or condition mediated by glycogen synthase kinase-3, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined in any one of claims 1 to 50.

61. A method of inhibiting glycogen synthase kinase-3, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined in any one of claims 1 to 50.
- 5 62. A method of modulating a cellular process (for example cell division) by inhibiting the activity of glycogen synthase kinase-3 using a compound of the formula (I) as defined in any one of claims 1 to 50.
63. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 10 50 in an amount effective to inhibit glycogen synthase kinase-3 activity.
64. A compound for use, a use, or a method as defined in any one of claims 51 to 63 wherein the disease state or condition is selected from proliferative disorders such as cancers and conditions such as viral infections, autoimmune diseases and neurodegenerative diseases.
- 15 65. A compound for use, a use or a method according to claim 64 wherein the disease state is a cancer selected from breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer, and non-small cell lung carcinomas.
- 20 66. A pharmaceutical composition comprising a compound of the formula (I) as defined in any one of claims 1 to 50 and a pharmaceutically acceptable carrier.
67. A compound of the formula (I) as defined in any one of claims 1 to 50 for use in medicine.

ABSTRACT**PHARMACEUTICAL COMPOUNDS**

The invention provides compound of the formula (I):



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wherein

X is CR⁵ or N;

A is a bond or $-(CH_2)_m-(B)_n-$;

B is C=O, NR⁸(C=O) or O(C=O) wherein R⁸ is hydrogen or C₁₋₄

10 hydrocarbyl optionally substituted by hydroxy or C₁₋₄ alkoxy;

m is 0, 1 or 2;

n is 0 or 1;

R¹ is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C₁₋₈ hydrocarbyl group;

15 R² is hydrogen, halogen, methoxy, or a C₁₋₄ hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy;

R³ and R⁴ are the same or different and each is selected from hydrogen, optionally substituted C₁₋₈ hydrocarbyl and carbocyclic or heterocyclic groups having from 3 to 12 ring members;

20 or R³ and R⁴ together with the carbon atoms to which they are attached form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S; and

R⁵ is hydrogen, a group R² or a group R¹⁰ wherein R¹⁰ is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C₁₋₄

25 hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, X¹C(X²), C(X²)X¹, X¹C(X²)X¹, S, SO, SO₂, NR^c, SO₂NR^c or NR^cSO₂; and R^b is selected from

hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, NR^c, X¹C(X²), C(X²)X¹ or X¹C(X²)X¹;

R^c is selected from hydrogen and C₁₋₄ hydrocarbyl; and

X¹ is O, S or NR^c and X² is =O, =S or =NR^c.

The compounds have activity as inhibitors of CDK and GSK kinases.

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Attorney or Agent: Philip E. Hansen

Registration Number: 32700

Customer Number Correspondence Address: 23405

23405

INVENTOR(s):

Primary Citizenship: British

Given Name: Andrew

Middle Name: James

Family Name: Woodhead

Residence City: Cambridge

Residence Country: GB

Address: 436 Cambridge Science Park, Milton Road
Cambridge , CB4 0QA GB

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